BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

Vol. XXIV.—No. 263.] BALTIMORE, JANUARY, 1913. [Price, 25 Cents

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THE BALTIMORE EPIDEMIC OF STREPTOCOCCUS OR SEPTIC SORE THROAT AND ITS RELATION TO A MILK SUPPLY.

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I.

In the Journal of the American Medical Association of April 13, 1912, there appeared a preliminary report of "An Epidemic of Septic Sore Throat" which prevailed in Baltimore in the preceding February and March. The infection was due to a streptococcus and was conveyed by an infected milk supply.

It is now possible to supplement the preliminary statement with the further confirmatory evidence of a study of 35 households representing 92 cases of the infection. These, together with a number of interesting cases, descriptions of which were communicated to me through the courtesy of many of my colleagues, furnish the basis of the present report.

The recognition of the epidemic followed when during the month of February, 1912, it became apparent to a number of practitioners of Baltimore that there was prevalent in the city an infectious disease of unusual severity of which the most constant sign was an inflammation of the fauces, in other words, a sore throat.

The malady was characterized by a sudden onset, high and irregular fever, inflammation of the fauces of varying degree, marked enlargement of the cervical glands particularly in the case of children, and a course much longer and attended with many more complications than the usual types of tonsillitis.

The results of cultures taken from patients' throats and of the examination of smears from the inflammatory exudates complicating the disease were strikingly uniform. Streptococci were always revealed. Thus, the discharge after paracentesis of the ear-drum in the case of a child 5 years old, ill of the infection, showed within leukocytes numerous pairs of Gram positive diplococci (Plate I, A), while a culture from the secretion of the opposite ear discovered the cocci in chains still retaining their diplococcic arrangement (Plate I, B). In 19 cases the bacteriologic examination was undertaken and each time a streptococcus was obtained, most often in pure culture. In this way it was recovered not only from the fauces and otitic exudate, but from suppurating lymph-nodes, from an abscess beneath the gastrocnemius muscle, from the peritoneum during laparotomy and from the blood of the femoral vein at autopsy.

The organism was studied at first in Dr. Charles Simon's laboratory by Dr. Simon and his associate, Dr. G. Howard White, and later by many other laboratory workers. These investigators have found that in the direct smears the organism often appears as an end to end diplococcus, intracellular in some specimens. Each pair seems surrounded by a halo but in the early specimens no envelope could be stained. Subsequently, however, capsules were repeatedly, though not invariably, demonstrated in smears from the inflammatory exudates. On culture media, however, the capsules are lost but the streptococcus again appears encapsulated when recovered from the blood of a mouse which had been previously inoculated. It is a Gram positive organism.

On agar it grows in dew-like droplets. It coagulates and acidifies milk, and in this liquid it develops in long chains with end to end arrangement and sometimes in tetrad form,

division having taken place in two planes (Plate I). The organisms are not dissolved by bile salts. Blood-agar plates show a hemolytic zone around individual colonies. In broth the cocci cause uniform turbidity. Inulin is not fermented.

A mouse inoculated intravenously with one of the strains died in 72 hours and from its blood an encapsulated streptococcus was recovered.

Heated in milk to a temperature of 145° F. for twenty minutes the organism is killed.

Almost simultaneously with the demonstration of this streptococcus Davis and Rosenow[1] published a description of a peculiar streptococcus obtained in the course of an epidemic of sore throat prevailing in Chicago just before the Baltimore

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The date of onset of the first case of "septic sore throat" in each of 35 households during February and the first half of March, 1912. These 35 households represented 92 cases of the infectious disease.

FIG. 1.

outbreak. It is obviously the same organism and the same infectious disease.

In a more recent communication Davis[2] concludes that the relation of this streptococcus of epidemic or septic sore throat to the ordinary streptococcus pyogenes is very close. Like the common hemolytic strain it causes multiple arthritis when injected into rabbits in very small doses. Occasionally, endocarditis results. In larger doses it kills guinea pigs and rabbits in from 24 to 48 hours. He ventures the opinion that they may be identical and that any differences which may exist may be caused by environmental factors.

A feature of the Baltimore epidemic which could not fail to attract attention was the large number of cases appearing suddenly within a few weeks in the month of February, 1912. A few cases apparently similar had been observed during the early winter months.

In the latter part of November and in December, 1911, I attended two children who were mildly affected with sore throat, and presented visible cervical glandular enlargements. They remained the only ones infected in the two households in which they lived.

On January 10, 1912, I saw a boy, 2 years old, suffering with tonsillitis. He subsequently developed marked symmetrical cer-

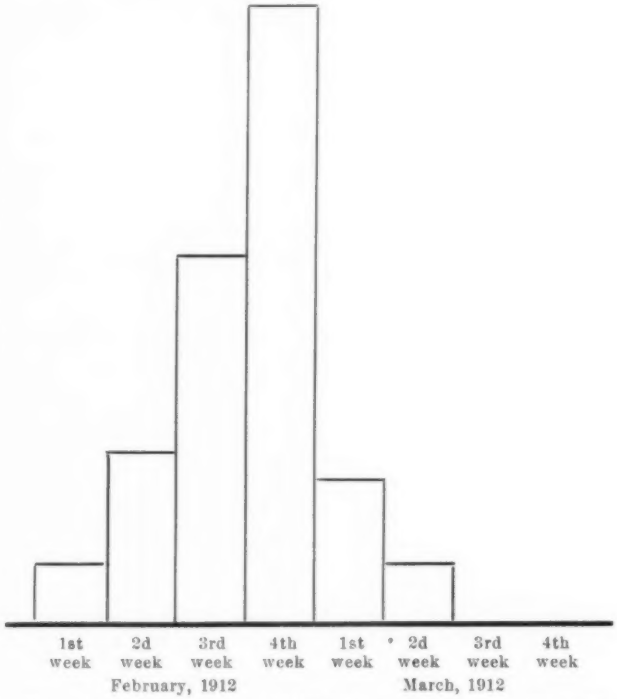


Chart showing the number of initial cases of "septic sore throat" in 35 households in February and first half of March, 1912, according to the weeks in which they occurred.

FIG. 2.

vical buboes and otitis media. The duration of his illness was 12 weeks. In quick succession his mother, an aunt and a maid were attacked by a severe sore throat. All three of these early affected households derived milk from the dairy which later came under suspicion.

In February, however, the cases multiplied, as the accompanying diagrams illustrate.

In Fig. 1 the squares represent the days of February and March, 1912. Each dot represents a household and is placed in the square corresponding to the day on which the first case of septic sore throat appeared in that family. It will be seen that the dots accumulate in the third and fourth weeks of February and then quickly disperse.

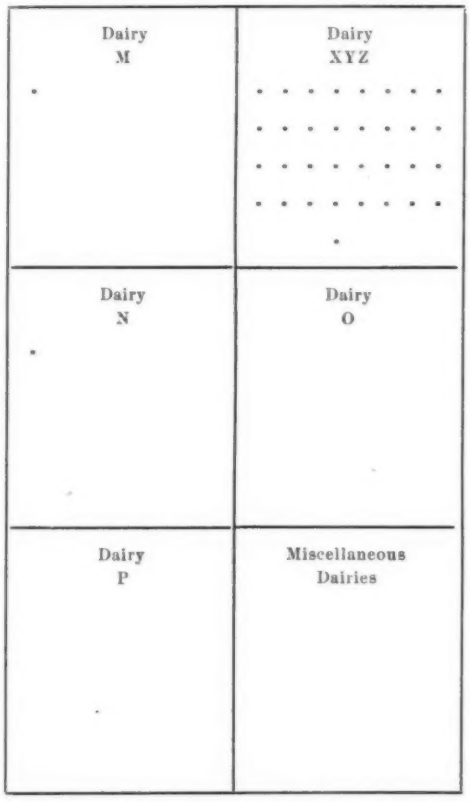
Fig. 2 represents a classification of the first cases in each of these households according to the weeks of February and March,

[1] Davis and Rosenow: An Epidemic of Sore Throat Due to a Peculiar Streptococcus. J. Am. M. Assn., March 16, 1912, 773.

[2] Davis, David J.: Bacteriologic Study of Streptococci in Milk in Relation to Epidemic Sore Throat. J. Am. M. Assn., June 15, 1912, 1852.

1912, in which they appeared. The column in the first week of February represents one household, the column in the second week four households, the column of the third week has risen to 10, while in the fourth week 16 households present the infection for the first time. Then the diminution in height of the column shows that by the middle of March newly infected households were not seen in my practice.

Throughout the latter half of March and the month of April there were many sore throats and in cultures made from these, streptococci were obtained, but clinically, with only one exception known to me, these cases were not accompanied by the septic complications which characterized the sore throat



The milk supply of thirty-five (35) households in which "septic sore throat" appeared in February and the first half of March, 1912.
The five dairies shown above are the largest in Baltimore.

FIG. 3.

now under discussion. Moreover, while the septic sore throats of February and the first half of March clearly exhibited a relation to the milk supply, these later and milder sore throats showed no traces of the milk route. They occurred in prosodemic fashion: namely, they appeared to be transmitted from individual to individual through various channels of communication.

The assumption that the infection might have been conducted through one of the general carriers of epidemic disease, such as milk, was ventured because of the explosive character of the outbreak, as illustrated by the foregoing diagrams, because of the wide distribution of the cases throughout the city and in view of the Boston outbreak to which reference will subsequently be made.

Accordingly there was instituted an inquiry regarding the milk supply of the 35 households in which the type of sore throat under discussion prevailed, with the noteworthy result graphically depicted in Fig. 3. It will be seen that 33 of the 35 infected households derived their milk from one and the same dairy, which is designated XYZ.

However striking this coincidence of dairy and disease may be, it is obvious that no valid conclusion can be drawn unless a comparison is made with the percentage of households in the city supplied by each of the various dairies. Such an inquiry could not be completed. It may be said, however, that the 35 households are distributed through the northern and western sections

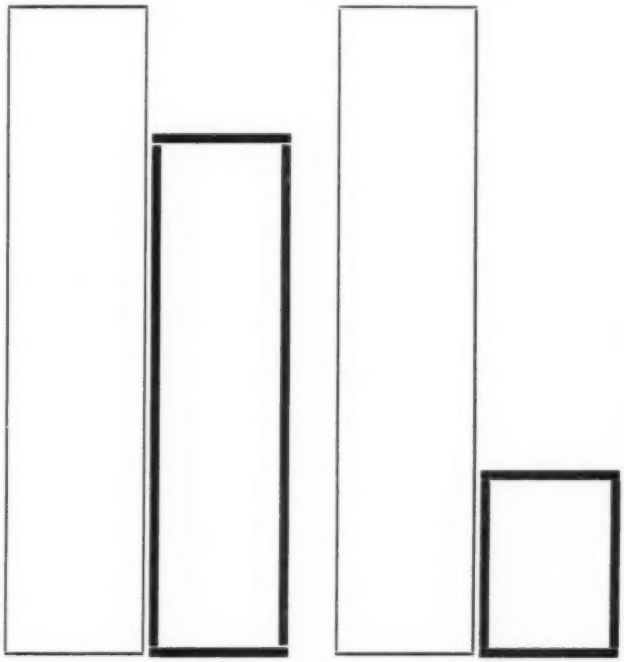

37 households supplied
by dairy XYZ
33 households affected; 90 cases.
37 households supplied
by dairies M, N, O, P, etc.
6 households affected; 6 cases.

Chart comparing two groups of households: the first, supplied by the XYZ dairy and the second, chiefly by dairies M, N, O, and P.
The heavy column represents the number of households in which "sore throat" appeared in February and the first half of March, 1912.

FIG. 4.

of Baltimore and those sections are supplied chiefly by the five dairies indicated in the diagrams. It is said that dairy M makes the greatest number of deliveries. The conclusion that the streptococcus infection travelled along the route of dairy XYZ is much strengthened by the succeeding diagrams.

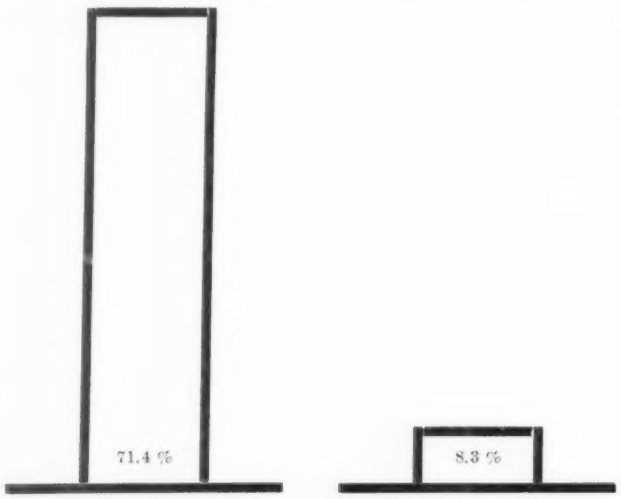
In Fig. 4 a comparison is drawn between two groups of 37 households each; the first supplied by dairy XYZ and the second principally by dairies M, N, O and P, the five being the largest dairies in the city.

The second group was selected in alphabetic order from a list of households on which I am in attendance, the only other basis of selection being that each of them should contain one or more children.

The heavy columns represent the number of households in which sore throat of any variety appeared in February and the first half of March, 1912. In the first group, supplied by dairy XYZ 33 households were affected with a total of 90 cases. In the second group of 37 households, chiefly supplied by dairies M, N, O and P, six households were affected, one case in each house.

The next diagram (Fig. 5) offers even more conclusive evidence. Here are represented the percentages of individuals suffering from sore throat during the period under consideration in two "homes" in the same section of the city, and occupied by trained nurses. The one was supplied by dairy XYZ and the percentage of nurses suffering from sore throat in this home rose to 71.4 per cent contrasting with 8.3 per cent in the home supplied by dairy O.

Additional and more gruesome evidence is furnished by the chart (Fig. 6) which represents the relation of 16 deaths from



The percentage of individuals suffering from "sore throat" in February and the first half of March, 1912, in two "homes" supplied by two dairies and occupied by trained nurses.

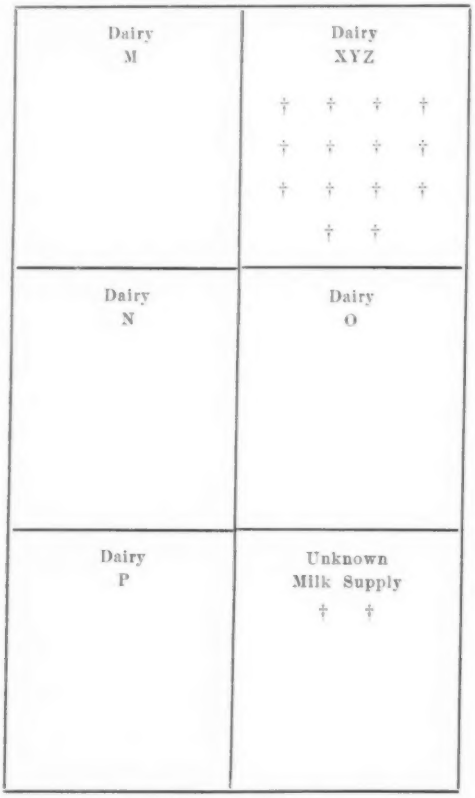
FIG. 5.

septic sore throat to the milk supply of the households in which they occurred. Fourteen are charged against dairy XYZ, while in the case of two the milk supply was unknown.

The first of these two is represented by Dr. Mayo's patient who died of streptococcus peritonitis at the Hospital for the Women of Maryland before the milk conduction was suspected. The second is an adult whom I saw with Dr. Finney, and who died two days later of peritonitis. She was too ill to interrogate at the time. In the XYZ square four crosses represent Dr. Rührah's patients. One each is furnished by Drs. Follis, Knox, Pancoast, Pennington, Shipley, Urquhart, and three are contributed by me.

For statistical purposes it would have been more satisfactory to have had a larger number of observations as a basis for the inquiry. With this object in view the United States Public Health Service offered its assistance, and accordingly Dr. Wade H. Frost was assigned to Baltimore, and on April 26, 1912, assumed charge of the work with the cooperation of the Baltimore Health Department. The epidemic was at an end when this investigation began, so that he experienced difficulty in selecting cases from the records of physicans at such a late date. Nevertheless, Dr. Frost was able to communicate to me the following note:

"I was to some extent disappointed, not being able to collect as extensive records as I had hoped to get. I gathered only about 600 cases, probably not more than a fourth of the total cases, very likely much less than a fourth . . . I have records of 31 deaths of which 26 were almost certainly, and the others quite



The relation of sixteen deaths from "septic sore throat" to the milk supply of the households in which they occurred.
The five dairies shown above are the largest in Baltimore.

FIG. 6.

probably due to this infection. My figures so far as I have analyzed them bear out your conclusions."[3]

[3] As this paper is submitted for publication Dr. Frost's elaborate epidemiologic study appears in The Public Health Report of November 22, 1912 (Vol. XXVII, No. 47). It is followed by a bacteriologic study of the outbreak by William Royal Stokes, M. D., and F. W. Hachtel, M. D. In their summary, attention is called to the inefficiency of the "flash" method of pasteurization which had been employed in the dairy up to the time of the epidemic. They venture the opinion that it is "reasonably" certain that the infection was caused by the streptococci of mastitis, cases of which were discovered in the herds supplying this dairy. No history of the presence of sore throats on the farms could be elicited.

Another link in the chain of circumstantial evidence that the streptococcus infection under discussion coincided with a milk supply was furnished by the proprietor of the dairy in question. Until this mishap the dairy employed the unreliable "flash" method of pasteurization. Following the recognition of the fact that the overwhelming number of primary cases developed along the route of his deliveries, the proprietor of the suspected dairy volunteered the information that during the rigorous winter weather of the latter part of January it was necessary to make repairs in the room in which the pasteurizer was situated, and for the time it was disabled. Certain it is that the milk was not heated during a period beginning January 28, 1912, and unpasteurized milk was delivered from that date through an undetermined part of February. It was thought that during such extreme cold the risk of incubating a pathogenic organism was practically negligible. It is, therefore, fair to assume that the organism was conveyed in raw or inadequately heated milk during the latter part of January and for some time in February, 1912. It was not until March 15 that, through the medium of the press, the public was advised to boil milk. During the ensuing week the proprietor of the incriminated dairy promptly changed its method of "pasteurization" from the "flash" system to the holding device.

The ultimate source of the infection was not discovered. The dairy derives its supply from numerous Maryland farms, but it is said that there was no evidence of an epidemic of either human or bovine disease on the premises of its tributaries.

In contrast with similar epidemics of streptococcus or septic sore throat in eastern Massachusetts[4] and Norway[5] where adults were chiefly affected, children were as frequently and more severely attacked in the Baltimore outbreak. Of the 92 patients 45 ranged in age from 4 months to 15 years, while 47 were between 16 and 65 years old. The oldest sufferer of whom I have knowledge, but who is not included in this list is a lady of 82 years. There were 61 females and 31 males in the series.

That children were most seriously ill is shown by the age distribution of the 16 deaths depicted in Fig. 7. Of these, 11 were children and 5 were adults.

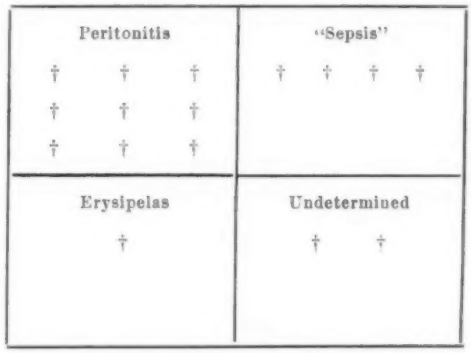
The incubation period was short, probably three days.

A nurse who came into one of these households on Wednesday, February 21, and who until then had not partaken of the milk of dairy XYZ, developed the sore throat Friday night, February 23.

The onset of the malady was sudden and was usually characterized by a chill or chilly sensations. The head, back and limbs ached. In an infant 23 months old the illness was initiated by a convulsion.

There was pain on swallowing. The appearance of the throat varied. Every type of faucial inflammation was represented. Perhaps the most frequent lesion was a dusky red discoloration of the fauces, a faucitis. In other cases there was a typical follicular tonsillitis, and in some, a membranous exduate resembling the lesion of diphtheria. Again, there was much peritonsillar infiltration which in some adults led to the formation of an abscess, to the development of a "quinsy" requiring surgical intervention. Absence of the tonsils did not preclude the development of the infection. In most of the severe examples of the malady the faucial lesion was of small import as compared with the constitutional disturbances.

The temperature rose rapidly; in one case, to 106.6° F. The curve was very irregular. The duration of the fever was largely dependent on the septic complications. At times, however, the fever continued after the faucial lesion had subsided and no other foci of inflammation could be detected to account for it. With the onset of suppurative processes the temperature assumed the usual intermittent type. Fig. 8 is a copy of the temperature chart illustrating the four weeks illness of a child 23 months old.



11 children. 5 adults.

The classification of sixteen deaths from "septic sore throat" according to the terminal event.

FIG. 7.

Convulsion at onset; follicular tonsillitis; cervical bubo; rhinitis; œdema of eyelids; double otitis media; cutaneous abscesses; recovery after a month's illness.

Irma K., aged 23 months, was suddenly taken ill on the night of February 29, 1912, with vomiting and fever.

On February 26 her mother suffered from a sore throat which confined to her bed for two days.

On March 1 about 6 p. m. she was seized with a convulsion. At half past six she lay in stupor with eyes rolled up and diverging to the right; temperature, 104.4° F., pulse 180. The throat appeared red, the tonsils were swollen, and a follicular exudate was present.

On March 3 (4th day) although the temperature rose to 106.4° F. the follicular deposit had disappeared; there remained only a dusky red discoloration of the fauces. A streptococcus had been cultivated from the throat.

The following day (5th day) a glandular mass was visible beneath the left angle of the jaw.

On March 6 (7th day) the nasal respiration seemed much obstructed and there was a muco-purulent discharge from the nostrils. The lids of the left eye were œdematous. At times the child appeared very stuporous but at intervals she was bright, even though the temperature remained high.

[4] Winslow, C. E. A.: Boston M. & S. J., December 14, 1911, 899; J. Infect. Dis., January, 1912, 73-112.

[5] Milk Epidemic in Christiania. Lancet, 1908, I, 107.

March 9, 1912 (10th day): "The child is pale and lies in stupor. The fauces are clear. The cervical bubo is still visible. The ear-drums are normal: the light reflex is apparent. Œdema of the eyelids has disappeared. Lungs are clear on percussion and auscultation. A systolic murmur is audible over all the cardiac valve areas. The temperature has ranged to-day from 101° F. to 103.8° F."

March 13 (14th day): "The cervical glandular mass has diminished in size, so that it is no longer visible. Nevertheless, the temperature rose to 103.1° F."

On March 17 there developed a left otitis media with spontaneous rupture, while six days later the right middle ear became involved.

The temperature remained normal on March 26, and the child began a rapid convalesence complicated, however, on March 31 by the appearance of a number of small superficial abscesses on the legs. She was able to leave the house after a month's illness.

On March 8 the father suffered from a sore throat and was confined to bed for three days.

The household was supplied by dairy XYZ.

Within the first week, usually in the case of children, the deep cervical lymphatic glands in the vicinity of the angle of the jaw enlarged so as to form visible tumors, often of considerable size and very tender. These buboes gave a characteristic picture to the disorder.

When bilaterally prominent the little ones looked like victims of Hodgkin's disease! The accompanying sketch (Plate I) depicts such an appearance. It is known that because of these swellings the condition was mistaken in several instances for mumps. The fate of the glandular masses was, in the majority, resolution. Even when of large proportion the bubo slowly subsided without the formation of pus. In six cases, however, suppuration occurred. Five of the patients were children and all recovered. The variable course of the adenitis is illustrated by the following case:

Faucitis; cervical bubo; relapse; diarrhœa; suppurative cervical adenitis; operation; recovery after six weeks' illness.

Irving S., aged 9 years, had been feeling ill several days previous to March 13, 1912, when he was seen suffering from fever and sore throat. The fauces were red; temperature 101° F. A glandular mass was visible beneath the right angle of the jaw. A week later the adenitis subsided, and although the boy looked pale he was able to leave the bed.

On April 3, 1912, about three weeks after the onset, he vomited, fever returned and he passed eight loose movements during the day, some of which were composed entirely of thick blood-stained mucus. The diarrhœa lasted three days.

At the end of the following week (4th) the cervical bubo which had long since subsided, returned. Eventually, fluctuation was present over the glandular mass and the temperature was intermittent. The abscess was incised on April 25, 1912, and from the evacuated pus a pure culture of a streptococcus was grown.

Coincident with his illness his sister, aged four years, had been similarly affected and underwent an operation for the relief of the cervical suppuration on April 10. Both children recovered.

The household was supplied by dairy XYZ.

In many children even after apparent recovery the buboes remained visible, a source of anxiety to the parents but of no discomfort to the children. It was apparent, too, that in the case of children who were markedly ill the size of the cervical bubo was of prognostic value. A large and persistent bubo was regarded as of good omen; for, in the fatal cases the glands were only moderately enlarged and quickly diminished in size.

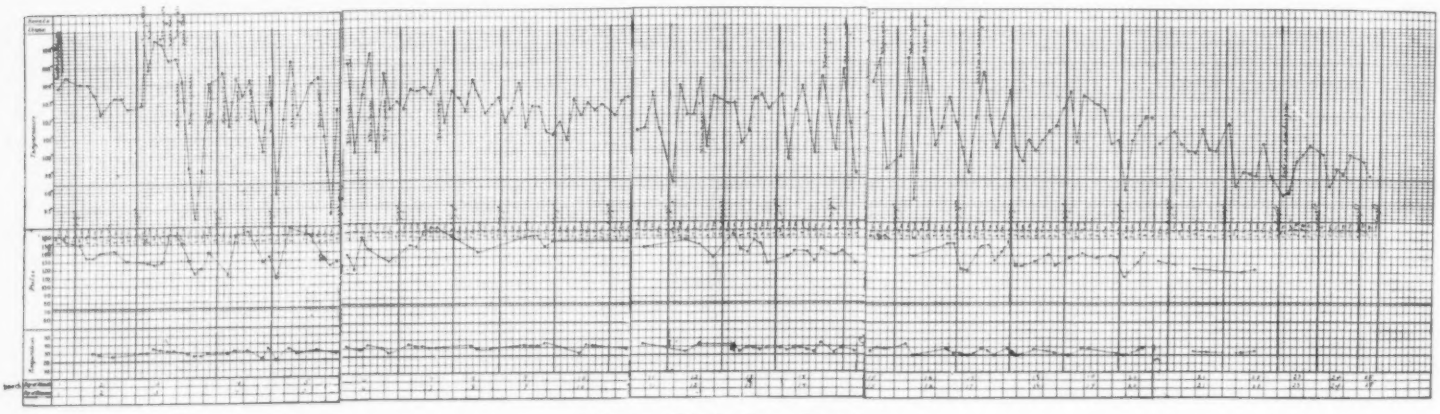


FIG. 8.—Septic Sore Throat.

Temperature chart illustrating the illness of Irma K. (see text).

There was no general glandular enlargement. The spleen and edge of the liver were frequently palpable beneath the costal margin. There was a leukocytosis but the differential count gave no noteworthy information.

Prostration was generally marked and the children became pale and thin and gave all the indications of having undergone a severe illness. Nevertheless, the course of the disorder was marked by great variation. In the same household there were those who were so mildly ill that they did not take to bed, while others exhibited all the signs of a profound septicemia for three or four weeks. Even in an individual case there was great irregularity. One day the patient seemed bright and convalescent; on the next, there might be a return of fever, somnolence, and increase in the size of the bubo.

The complications and sequelæ were very numerous. Vomiting at the onset was common. Abdominal pain without sub-

CHILDREN EXHIBITING THE CERVICAL ADENITIS OF SEPTIC SORE THROAT.

sequent development of general peritonitis was a disquieting symptom.

There are notes of two children who cried out with pain in the abdomen. One of them, a girl five years of age, presented abdominal tenderness, which together with muscular rigidity was most marked over the right iliac fossa. The day after the appearance of these symptoms and signs she developed an otitis media and the abdominal pain disappeared.

Enteritis was encountered several times. Glossitis and ulcerative stomatitis were complications in the fatal case, the report of which was communicated to me by Dr. Wells.

Follicular tonsillitis; cervical adenitis; ulcerative stomatitis; glossitis; death on the 10th day.

Virginia T., aged 4 years, complained of sore throat on February 27, 1912. She was seen by Dr. Wells on March 1, when she presented a follicular tonsillitis with enlargement of the cervical glands. Temperature 103.5° F. During the ensuing week the mucous membrane of the right cheek ulcerated, the loss of substance extending beneath the tongue on that side. The tongue swelled so that it almost filled the entire oral cavity. The child could be fed only with greatest difficulty. The temperature ranged from 105° F. to 106° F. Early on the morning of March 7 the little girl vomited and died a few minutes after the attack. The household was supplied by dairy XYZ.

Dysphagia was a noteworthy symptom in a patient observed by Dr. William T. Watson. The following are his notes:

Faucitis; supraclavicular bubo; dysphagia.

"Mrs. S. had an inflammation of the tonsils, soft palate and uvula which ran a shorter course than a majority of the cases. She had slight involvement of the glands and jaw. After a few days the superficial cervical glands above the outer end of each clavicle became very much enlarged, so that the swollen masses could be seen across the room. The skin over each of them became red but no abscess formation occurred. As they were subsiding the patient complained of pain along a line corresponding to the whole length of the œsophagus which could be felt any time she swallowed food or liquid. This persisted for a number of days."

It is of interest to note in passing that both glossitis and this peculiar dysphagia were described in the Christiania epidemic.[6]

Abscess formation occurred in the peritonsillar tissue, in the ear, in the cervical glands and in the superficial and deep tissues of the legs.

It is noteworthy that herpes was absent. Preble[7] has called attention to this fact in giving the clinical history of the Chicago epidemic.

Rhinopharyngitis was often encountered. During the period covered by the epidemic there was occasionally observed a case of bronchitis with râles chiefly unilateral, accompanied by slight dyspnœa and prolonged fever. Although there is no bacteriologic evidence to substantiate the statement, the opinion is ventured that these cases may have represented examples of bronchitis or bronchopneumonia due to the streptococcus.

[6] Loc. cit.

[7] Preble, Robert Bruce: J. Am. M. Assn., June 22, 1912, 1933.

In rare instances there was severe laryngitis. In regard to this complication Dr. Watson has furnished the following description:

"In two cases the disease of the tonsils and palate had spent its force and the patient was apparently recovering when suddenly there was difficulty in swallowing and the mirror showed extensive laryngeal involvement. In one such case the epiglottis could be seen, by simply depressing the tongue, as a large round gelatinous looking mass. In the other case the epiglottis became a large red mass overhanging the larynx and hiding the glottis."

The slow pulse which Preble[8] mentions as one of the most striking features of the Chicago cases was an infrequent sign in the Baltimore patients.

A girl, 16 years of age, the patient of Dr. Michael Abrams, suffered from sore throat on March 15, 1912. She developed huge bilateral cervical adenitis which did not suppurate. Although the temperature was 103° F. the pulse was only 62.

One patient in this series exhibited an erythema over the legs in the second week of her illness, and at the same period in the course of the disorder in one of Dr. Watson's patients a similar rash resembling the eruption of scarlet fever, lasting only a few hours, appeared over the body and extremities.

Erysipelas was present in three of the children. It was fatal in the case of an infant four months old. The second child, a boy of 23 months, recovered from the cutaneous inflammation, but subsequently died of peritonitis. The third example of erysipelas is remarkable because of the point of departure of the process.

Erysipelas of the vulva without history of antecedent sore throat; three cases of sore throat and cervical adenitis in the household; recovery.

Carolyn F., aged 2 years and 9 months, complained on April 11, 1912, of pain on voiding urine.

On February 17 a maid in the household had suffered from a "very sore throat" and marked swellings about the region of the angle of the jaw. She had thought she was "getting the mumps."

On February 21 a second maid had been similarly affected. These two girls were confined to bed for three weeks.

On February 22 Carolyn's sister, aged 4½ years, was taken ill with sore throat and swollen glands.

There is no history of sore throat in the case of Carolyn although a small gland is palpable beneath the right angle of the jaw.

The fauces appear normal. Temperature, 105° F. The mother calls attention to the condition of the vulva. The left labium is swollen, red and very tender, and it is evident that the dysuria bears a relation to this localized inflammation. There is no vaginal discharge and the urine is clear.

On April 13 the temperature continued high (105° F.); the left labium became similarly affected. Dr. Guy L. Hunner saw the child with me, but neither of us could give a satisfactory interpretation of the state of the vulva.

The following day (April 14) the right labium appeared practically normal. The left was also less swollen and less red but extending from the vulva over the antero-external aspect of the left thigh around to the left buttock there was an area over which the skin was rose red and tender. There was a sharp

[8] Loc. cit.

line of demarcation close to the anus. The child cried with pain on making an attempt to evacuate the bowel. The condition was now entirely clear: the inflammation of the vulva was erysipelas.

On April 23, 1912, the skin was desquamating. The child had recovered.

The household's milk was supplied by dairy XYZ.

There were two cases of nephritis among the 92 patients.

Four of the children showed a unilateral œdema of the eyelids.

Inflammation of the serous membranes was observed and included arthritis, tenosynovitis and peritonitis.

There are notes on seven cases of arthritis, four of which occurred in the present series of 92 patients. It was usually polyarticular and prolonged the illness, in some cases, several weeks. It was not associated with endocarditis and the arthritic exudate was never purulent.

Tonsillitis with exudate; otitis media; multiple arthritis; recovery after an illness of two months.

Mrs. M. K., aged 49 years, presented on March 5, 1912, an exudate on both tonsils and moderately enlarged cervical glands. Subsequently she developed otitis media and at the end of two weeks multiple arthritis indistinguishable clinically from the type which is usually described as characteristic of "rheumatic fever." She was confined to bed with this complication for six weeks.

In the same house a son and a maid had suffered from sore throat, the latter part of February. Dairy XYZ furnished the milk of the household.

Peritonitis was the terminal event in the majority of the 16 fatalities, as Fig. 7 illustrates. Of the nine who died of peritonitis six were children and three adults. How quickly disaster followed inflammation of the peritoneum is illustrated by the following history:

Faucitis; no cervical bubo; diarrhœa; peritonitis; death on the fourth day of illness.

John H., 3 years old, whose sister was suffering from the same streptococcus septicemia, and who himself had been well the previous day, complained on March 4, 1912, of a sore throat.

At 10 a. m. his temperature was 104.4° F. The anterior pillars of the fauces were of a dusky red color. The tonsils were not enlarged, and there was no exudate. The cervical glands were slightly enlarged. At 7 p. m. the temperature was 106° F. During the following day he was delirious and suffered from diarrhœa, having passed 10 small yellow liquid stools.

A culture taken from the throat disclosed the streptococcus previously described. On the morning of the third day, March 6, he was much improved, bright and crying for cake and permission to leave the bed. The rectal temperature at 10.30 a. m. was 100.4° F. Yet, at noon he vomited and the temperature rose so that at 4.30 p. m. it registered 106° F. He had had three liquid stools during the day. Examination of the ears was negative. At 5.30 p. m. he looked very ill. His pale skin presented a purplish mottling. The pulse was of small volume, the abdomen was tender. He begged for water.

It was given repeatedly in small quantity, but was vomited each hour. The child retained consciousness throughout the night although the radial pulse was not palpable; the abdomen became distended, vomiting continued, and at half past eight on the morning of the fourth day of his illness he was dead.

Laparotomy was performed on three adults suffering from this terminal peritonitis. In one of these cases the exudate was purulent; in the other two, a general fibrinous inflammation was present. A streptococcus was isolated from the peritoneal fluid of all.

At the beginning of the Baltimore outbreak of septic sore throat the disorder was diagnosed indefinitely as "grip," and it was not until several fatalities had followed sore throats that the unusual character of the epidemic infection became evident. Thereafter, the diagnosis was based chiefly on the clinical picture and the course of the malady. Fever persisted longer than in the usual types of sore throat. In many cases the severe constitutional disturbance was out of proportion to the intensity of the faucial lesion.

From the faucial lesion alone the diagnosis could not be made. Bacteriologic examination of the throat, disclosing on smears diplococci and on culture media chains of cocci, was easily and quickly carried out and confirmed the nature of any suspected faucial inflammation.

The fauces appeared to be the portal of entry, but occasionally there arose the question as to the possibility of streptococci gaining access to the body through a channel other than the throat. Carolyn F., who suffered from erysipelas without a sore throat having been detected, is a case in point.

From the foregoing considerations it will be seen that the cases which were clinically designated "septic sore throat" fall into three groups.

The first group is characterized by inflammation of the fauces associated with marked visible enlargement of the cervical glands.

There is a second group with or without the physical signs just mentioned, but presenting some metastatic septic or streptococcic complication, such as erysipelas, arthritis, abscesses or peritonitis.

In the third group are included cases of sore throat occurring in households in which one or both of the first two types prevailed.

It was not possible to establish an accurate prognosis in the individual case. The history of John H. illustrates the unexpected fatal issue. Large and persistent cervical buboes warranted a favorable outlook.

Of the 92 patients three died. Because of my interest in the epidemic Dr. Finney's patient dying of peritonitis came under observation two days before death and can properly be excluded from the estimate of the death rate in this series. The rate of mortality would then be about two per cent.

The treatment of sufferers from "septic sore throat" did not vary from the usual management of febrile patients. No advantage seemed to be derived from direct faucial medication.

Aspirin (acetylsalicylic acid) was used in almost every case and brought temporary relief from the pain in various parts of the body. Hexamethylenamin was frequently administered but without apparent beneficial result. Vaccine therapy was not employed.

Realizing that the cervical buboes, even when of large di-

mensions, usually disappeared spontaneously, surgical intervention was not practised unless fluctuation was distinctly appreciable.

II.

That milk is a medium of transmission of some infectious diseases to man is no longer doubted. There come to mind at once tuberculosis and typhoid fever and the less familiar milk epidemics of scarlet fever, diphtheria and gastroenteritis. But, it is not generally known that the first clinical record of probable conveyance of disease through milk was that of Sagar, who in 1764 ventured the opinion that a number of throat affections and aphthous ulcers were due to drinking the milk of a certain cow.[9]

Nevertheless, since that early date, records of milk-borne sore throat outbreaks have been comparatively rare. The Baltimore epidemic is the second recorded American outbreak of severe throat infection connected with a milk supply.

The first is the eastern Massachusetts epidemic of May, 1911, described by C. E. A. Winslow.[10] Simultaneous with the publication of the preliminary report of the Baltimore streptococcus infection there appeared a note on the probable spread of a similar epidemic in Chicago through milk.[11]

Similar outbreaks have been more frequently observed in Great Britain, where the affection is often described as "septic sore throat," and it is from English source that this term has been adopted.

Recently 18 English epidemics have been gathered and critically examined by Dr. William G. Savage.[12] They date from the outbreak in March, 1880, among the boys at Rugby School to the large epidemic of April, 1905, at Colchester, carefully studied by Dr. Savage himself.

With the addition of the Norwegian report[13] the recorded milk-borne sore throat outbreaks now number 22. In practically all the symptomatology is the same. Whenever a bacteriologic examination was made a streptococcus was found in cultures from the throat and other foci of inflammation. In nearly all the evidence that the infective agent was spread by milk is fairly satisfying, but in a great number the final source of the infection is by no means clear.

There is a group embracing 10 epidemics in which there is reasonable certainty that the infection was derived from a cow or cows suffering from mastitis or from ulcerated teats.

There is a second class including five outbreaks in which it is possible to assume that the milk was polluted by contact with individuals suffering from sore throat. But in seven the evidence is not satisfactory enough to venture even an hypothesis as to the origin of the infection.

The epidemic at Christiania in the fortnight of March, 1908, embracing 548 reported cases, can probably be admitted to the first division, since it is stated that "it (the outbreak) was speedily traced to the milk supply of one dairy and thence to a cow with a diseased udder. The cow was slaughtered and a bacteriological examination of the abscess found in the udder led to the isolation of streptococci in every way identical with the streptococci obtained from patients suffering from the epidemic."[14]

According to Dr. Savage's critique of the Colchester epidemic of April, 1905, involving at least 600 persons it is "nearly certain" that here, too, the infection was of bovine origin.

The milkman M. (whose dairy was implicated) obtained his milk from 6 farms . . . Only on farm B were human cases of illness or disease amongst the cows met with. Upon this farm a cow was found in the shed, with the others, suffering from mastitis of one quarter, and which had been noticed to be ill since about April 19. The milk of this cow was being added to the milk up to the time of April 27. The cessation of the outbreak corresponds with the exclusion of the milk of this particular cow . . . The first illness on the farm was that of the farmer himself, who suffered from a severe sore throat, which confined him to bed for 3 or 4 days. He never milked the cows, and said he had very little to do with them. The onset of his illness was April 17, a date which coincided with other cases in the town. This, with other facts renders it nearly certain that he was infected from the milk and was not the source of infection of the milk.[15]

On the other hand, as a result of Winslow's study of the eastern Massachusetts epidemic of septic sore throat he concludes that "probability points to the infection of the milk from the human cases" which were known to be abundant on and in the neighborhood of the farm from which the distributing dairy derived its supply.

The study is based on 1043 cases. The epidemic began on May 8, 1911, rose to a maximum on May 14 and practically ceased after May 28. Forty-eight deaths were attributed to the infection. The cases followed the milk supply of a "carefully supervised" dairy to which farms in the towns of Southboro and Marlboro were tributary. The peculiar sore throat under discussion prevailed in prosodemic form in the towns of Hudson, Marlboro and Southboro during April and May, and in the second week in May it appeared in epidemic fashion in Boston, Brookline, Cambridge, Marlboro and Southboro along the route of the dairy above mentioned. No bovine disease was discovered on the farms, and although there was no record of direct contact of a patient with milk it was thought probable that the infection was due to a human carrier. Dr. Theobald Smith examined 4 cultures made from the internal organs in typical septic cases and isolated streptococci, all apparently of the same type.[16]

Another example of possible human origin of a streptococcus infection of milk is afforded by the report of the Guilford epidemic of 1903 based on a study of 98 infected households.

The outbreak dated from the last week in September to the first of November. The proprietor of the incriminated farm suf-

[9] Quoted by Stokes, Wm. Royal and Clement, A. W.: An Epidemic of Purulent Inflammation of the Milk Ducts Affecting Seventy Cows. Maryland M. J., January 9, 1897.

[10] Loc. cit.

[11] Miller, J. L. and Capps, J. A.: Epidemic of Sore Throat due to Milk. J. Am. M. Assn., April 13, 1912, 1111.

[12] Savage, William G.: Milk and the Public Health, 1912, 91.

[13] Loc. cit.

[14] Loc. cit.

[15] Milk and the Public Health, 1912, 98; Public Health, 1905-6, XVIII, 1.

[16] Loc cit.

fered from "quinsy" the middle of September. His illness antedated the outbreak. He assisted at the milking. Four of the 20 cows on the farm suffered from mastitis, and streptococci virulent to mice were isolated from their milk. It was suggested that they were infected by the farmer and that the mastitis supplied a continuous source of the infection which extended six weeks beyond the illness of the farmer himself.[17]

Capps and Miller's[18] able investigation of the epidemic of streptococcus sore throat in Chicago, December, 1911, disclosed similar conditions on a larger scale: namely, mastitis was epidemic among the cows supplying the milk to the suspected dairy (dairy X), and sore throat of the epidemic type was prevalent among the farmers and milkers. Virulent streptococci with similar cultural properties were isolated from the inflamed udder of a cow and from the human faucial lesion.

The epidemic involved probably 10,000 persons in Chicago. Of 622 patients suffering from septic sore throat 87 per cent used the milk of dairy X. Of 19 fatal cases 79 per cent had partaken of this milk. Although tonsillitis was prevalent in the state of Illinois it was only in Batavia that there was an epidemic similar to that of Chicago, but here the X milk was collected from the farms and pasteurized. Batavia was also in part supplied with this milk. Mastitis involving 4.6 per cent of the cows supplying the dairy was epidemic during the winter months and was worst about the Christmas holidays. Sore throat of the epidemic type was also prevalent on the farms and in this locality.

Davis[19] isolated the peculiar streptococcus to which reference has been repeatedly made both from the milk of a cow exhibiting chronic mastitis and from the fauces of a girl on the same farm, who had been ill with sore throat and arthritis.

The dairy employed the "flash" method of pasteurization by which the milk was momentarily raised to 160° F., but large fluctuations of temperature were demonstrated on the pasteurizer's thermal charts. On several days a minimum temperature of 130° F. was recorded. There was a distinct relation between the days on which the pasteurizer was most inefficient and the subsequent days on which great outbreaks of sore throat occurred.[20]

A final conclusion as to whether the bovine mastitis was the primary source of infection or whether the udder disease was secondary to the milkers' sore throat or whether the bovine and human infections were independent could not be reached in a consideration of the Chicago epidemic.

Thus are raised two questions: are the streptococci of bovine mastitis pathogenic to man, and, can streptococci found in instances of human sore throat produce mastitis in cows? Savage[21] has investigated the problem with the following interesting results: Of 36 cases of mastitis in cows 68 per cent were due to streptococci. Eighty per cent of these streptococci could be classified as a common type designated as *streptococcus mastitidis*. Nevertheless, it is important to note that in several cases "quite different streptococci" were cultivated. In 16 cases of human sore throat the most prevalent type of organism was what has been designated *streptococcus anginosus*, while a second type was identical with *streptococcus pyogenes*. Now, it was found impossible to differentiate the *streptococcus mastitidis* and the *streptococcus anginosus* either morphologically or culturally, even when the various sugar-alcohol tests were used. While the bovine streptococcus was, as a rule, nonpathogenic to rodents, the *streptococcus anginosus* frequently caused death in mice. Still, Savage considers this distinction one of degree rather than of kind. The functional capacity of the streptococci was further investigated in a series of experiments on the teats of goats. Three streptococci from cases of mastitis in cows set up mastitis in the goats in every instance. Seventeen strains from human origin all failed to evoke mastitis in another series of goats. Two streptococci derived from a case of Ludwig's angina and from a case of acute epiphysitis produced some degree of mastitis in these animals.

Although the experiment is far from conclusive, it is of interest to add that without ill effect Savage infected his own throat with massive doses of the *streptococcus mastitidis* freshly isolated from the mastitis of cows.

Furthermore, he calls attention to the fact that while bovine mastitis is common, sore throat due to milk is rare. Therefore, Savage concludes that the organisms causing the great majority of cases of bovine mastitis are not virulent to man, but that in certain uncommon cases inflammation of the udders of cows may be provoked by streptococci pathogenic to human individuals.

After all is said, the problem of the differentiation of streptococci remains unsolved. It would be of greatest value if there were discovered some convenient method of determining the source and functional characters of these organisms. Certain practical conclusions, however, remain unaffected. Cows suffering from mastitis must be excluded from a milk supply and human individuals suffering from sore throat must be prohibited from handling the milk at any stage from production to delivery. Since these measures can be carried out only in theory, effective pasteurization of a city's milk supply is the only satisfactory method of averting the possibility of such an outbreak of septic sore throat as occurred in Baltimore during the winter of 1912.

III.

The lessons which can be deduced from the foregoing discussion are embodied in the following conclusions:

1. The undue prevalence of sore throat and other influenzoid affections should be reported to the Municipal Health Department for investigation as to the possibility of milk conduction of the infection.

2. A streptococcus infection when it is introduced into a community through milk possesses an extreme virulence and

[17] Brit. M. J., 1903, II, 1492.

[18] Capps, Joseph A., and Miller, Joseph L.: Chicago Epidemic of Streptococcus Sore Throat and Its Relation to the Milk Supply. J. Am. M. Assn., June 15, 1912, 1848.

[19] Davis, David J.: Bacteriologic Study of Steptococci in Milk in Relation to Epidemic Sore Throat. J. Am. M. Assn., June 15, 1912, 1852.

[20] Capps, Joseph A: The Rôle of Milk in the Causation of the Chicago Epidemic of Sore Throat. J. Am. M. Assn., November 9, 1912, 1715.

[21] Milk and the Public Health, 1912, 107-111.

may produce a clinical picture characteristic in some aspects and complicated in many.

3. It is possible that raw milk from any dairy though carefully produced and handled may at some time convey a streptococcus infection.

The dairy, along the route of which the overwhelming number of cases of septic sore throats developed in the eastern Massachusetts epidemic, feeling secure in the elaborate precautions exercised to produce clean milk, did not employ pasteurization. For 28 years this dairy had been furnishing its product to Boston, without mishap, when in May, 1911, the outbreak occurred.

4. From a study of the American epidemics of streptococcus or septic sore throat the importance of thorough pasteurization of clean milk in its final containers under efficient official inspection is clear.[2]

[2] Jordan, Edwin O.: The Case for Pasteurization. J. Am. M. Assn., October 19, 1912, 1450.

In the course of the Chicago epidemic the 70 occupants of the children's wards at the Michael Reese Hospital escaped without developing a single case of sore throat. Fifty-three per cent of the nurses of this hospital were attacked. Both the children's ward and the nurses' home were supplied by dairy X. There was this important difference: the nurses drank the milk "pasteurized" by the dairy's "flash" method, while the milk delivered to the children was pasteurized effectively by the holding system in the hospital itself.

5. If by accident the pasteurizing plant of a dairy is disabled the dairy should notify its patrons to boil the milk.

6. When the price of pasteurized milk is prohibitive it is suggested that the practice of boiling milk should be advocated or instruction in home pasteurizing[3] should be given in medical dispensaries, by visiting nurses and by physicians.

7. Finally, it is obvious that milk inspection as at present conducted is inadequate.

[3] Circular 197, Bureau of Animal Industry, U. S. Dept. Agric., Washington, D. C., April 19, 1912.

THE EFFECT OF HYPERSENSITIVENESS TO A TUBERCULO-PROTEIN UPON SUBSEQUENT INFECTION WITH BACILLUS TUBERCULOSIS.

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Tuberculosis is a disease of man and of cattle, widespread and devastating. Practical interest, therefore, attaches to the question whether it is possible to obtain a usable protective inoculation against it. Such a practical vaccination for man has not been found, but since the work of Von Behring demonstrated the possibility of artificial immunization in cattle with bovo vaccine, many inoculation preparations have been made and various modes of administering them have been devised.

Römer,[1] in a series of monographs, has published the effects of a primary tuberculosis in animals upon the course of a second infection with tubercle bacilli. Guinea-pigs, sheep and cattle already suffering with inoculation tuberculosis, were reinfected by the cutaneous or by the intracutaneous route, and carefully studied along with control animals. He found that the primary infection was protective, conferring "complete immunity to small reinfecting doses, diminishing the infectiousness of reinfecting doses of moderate size, and leading to a lack of immunity when moderately large doses were injected." Further "to massive amounts of tubercle bacilli, an already tuberculous host is more sensitive than is a normal animal succumbing with the symptoms of acute hypersensitiveness." The one biological reaction constantly present in the animals used in the reinfecting experiments was hypersensitiveness, —hypersensitiveness not only to tuberculin, but to the tubercle bacillus itself. In this condition Römer believes the possible, even the probable, immunization mechanism exists. It is of great interest that he differentiated between hypersensitiveness to the tubercle bacillus (*Tuberkelbacillen-Überempfindlichkeit*); and hypersensitiveness to tuberculin (*Tuberkulin-Überempfindlichkeit*); a differentiation independently recognized by Calmette.[2] This difference between hypersensitiveness to living tubercle bacilli and to tuberculin, both authors consider a fundamental difference and not merely a quantitative one.

Sata,[3] on the basis of immunization experiments made on horses, cattle, guinea-pigs and rabbits, with living and with dead bacilli, as well as with extracts of pulverized organisms, claims to have demonstrated a certain connection between "the hypersensitiveness which developed, and the production of antibodies." "Where hypersensitiveness develops," says Sata, "there immunity appears; therefore it is justifiable to conclude that immunity has developed wherever allergy exists, and since hypersensitiveness may be produced by the toxins of the bacilli, as well as by the bacilli themselves, immunity may be stimulated by the injection of these toxins." Sata did not prove a causal relationship between the hypersensitive state and the immunity, and so far as his experiments are concerned, the opinion may still be entertained that the two conditions are coexistent, without having necessarily a causal interdependence.

Little work has been published to demonstrate the relation of allergy alone to immunity.

Rosenau and Anderson[4] sensitized guinea-pigs with extracts of *B. typhosus* and of *B. coli* and found, in each instance, that the animals so treated were immune to amounts of the respective organisms, fatal to normal guinea-pigs.

In 1907 Vaughan and Wheeler[5] injected guinea-pigs with from 15 to 200 mgm. of tuberculo-protein ("cellular substance," "cell residue," etc.) and one month later inoculated the same animals "with a loop of an avirulent culture of bacillus tuberculosis." They observed that the intraperitoneal

injection of the protein had sensitized the animals so that "the bacilli of the second dose were broken up so rapidly and their poisonous constituents set free so speedily that the animals died." In other words Vaughan and Wheeler demonstrated that as a result of hypersensitiveness to tuberculo-protein, hypersensitiveness to tubercle bacilli had developed.

Duval and Couret,[6] in attempting to produce experimentally the lesions of leprosy in the monkey, failed to do so, until they had sensitized their animals with "large numbers" of leprosy bacilli, "injected at given intervals for a period of months." They stated "that infection is more likely to follow where sensitization is first established, is definitely proved by the specific experiments that we have carried out in a number of laboratory animals. The first injection we assume sensitizes the animal and it may consist of either killed or viable lepra bacilli." Again, "in our experience it has been extremely difficult to produce in the lower animals more than a transient localized lesion with human leprous material, rich in the specific bacilli, unless the animal is first sensitized, when lesions histologically identical with those produced by pure cultures are easily induced." These observations, so far as we have been able to learn, are the first that would indicate definitely that sensitization with a specific protein can diminish the resistance of an animal to infection with the organism from which the protein was derived.

Krause,[7] in 1911, published the results of a small series of inoculations of living tubercle bacilli into sensitized and into refractory guinea-pigs. The animals, after sensitization with a tuberculo-protein, made according to the method of Baldwin, were each given a subcutaneous injection of 0.1 ccm. of an emulsion of tubercle bacilli, which contained an average of one bacillus to every one or two fields. Sixty-two days after inoculation, the infected animals were killed by a blow on the head. Krause, interpreting his results on the basis of macroscopic tuberculosis, concludes that the refractory animals suffered most "showing the disease pretty well disseminated, and far more tuberculosis than any of the animals that had not been intoxicated, and than any of the controls." The animals that had been sensitized all developed tuberculosis and "as a general thing, the more protein the animal received during preliminary treatment, the less was the resultant infection." In summary he concludes: "Sensitization of non-tuberculous guinea-pigs with tuberculo-protein does not alter their resistance to experimental tuberculous infection. Sensitization to tuberculo-protein and relative immunity (increased resistance) to infection can occur coincidently in the same animal. Resistance to infection is markedly lowered during the period that a sensitized animal is suffering from symptoms of anaphylactic shock."

In order to test the validity of the assertions of Römer and of Sata, that the hypersensitive state was responsible for the immunity that developed in their animals, the course of infection in animals in which sensitization had been produced apart from infection was noted. This seemed worth while, since if sensitization with non-toxic products led to immunity to infection with living tubercle bacilli, an inocuous prophylactic vaccination might be developed for use in man.

The Influence of Hypersensitiveness to a Tuberculo-Protein Upon Infection with Tubercle Bacilli.

The work of Römer (*l. c.*) showed that a primary infection with living tubercle bacilli confers an immunity to reinfection with the organism. Inasmuch as Römer found that hypersensitiveness was the one biological reaction constantly present, he inclined to the view that this condition of altered response might be the protective mechanism which made the animals immune to a second infection. In spite of the apparent proof that the hypersensitive state was the protective factor, certain other possibilities were at once evident. The mere fact that the known antibodies tested for were present only inconstantly, whereas hypersensitiveness was always demonstrable, did not necessarily show that the latter was the true immunizing influence. It is conceivable that other antibodies, the methods of demonstrating the presence of which are not yet known, might have been present. The hypersensitiveness might have been coexistent with and still not causally related to the immunity, or it might have been a baneful factor, in a measure diminishing resistance to infection.

During the four months preceding our interest in this problem, we had been working with a tuberculo-protein and studying the hypersensitiveness developing in guinea-pigs and in rabbits treated with it. It occurred to us, therefore, that the interrelation of hypersensitiveness to this protein and infection with tubercle bacilli, might readily be determined, inasmuch as in animals so treated, antibodies other than sensibilisin would be lacking or present only in minimal quantities.

The tuberculo-protein used for sensitization in the following experiments was made according to a modification of the technique recommended by Baldwin.[8] Three strains of human type tubercle bacilli, H39, received through the courtesy of Dr. A. K. Krause, of the Saranac Laboratory, and Hα and Hβ, isolated from the sputa of two patients ill with tuberculosis, were inoculated into a number of flasks containing 5% glycerine broth. At the end of several weeks the broth was removed, the bacilli washed several times with 0.85% salt solution, then dried in vacuo and thoroughly ground in a mortar. The pulverized mass was then suspended in water in the proportion of 1 gm. of bacillary powder in each 15 ccm. of distilled water, and extracted for 48 hours at 55° to 60° C. The suspension was filtered through a Berkefeld bougie, and the protein, precipitated from the amber colored fluid with ten volumes of absolute alcohol, was dried in vacuo. The powder so obtained is readily soluble in water and, as the result of numerous experiments, it was found that 10 to 15 mgm. of the material inoculated into the peritoneal cavity of a full grown guinea-pig, is required constantly to produce active sensitization.

It is of some importance to note that the protein thus obtained varied considerably in its sensitizing power, in spite of the fact that great care was taken to employ the same technic in the making of each supply of the preparation. This protein, too, is practically non-toxic, an intraperitoneal injection of as much as 200 mgm. in single or in divided doses failing to cause symptoms when injected into the peritoneal cavity of guinea-pigs of 300 gm. weight.

For inoculation, suspensions of cultures of Hα were made as follows:

The organisms grown in 5% glycerin broth were rubbed on the wall of an Erlenmeyer flask, a small amount of sterile salt solution was added, and after the addition of sterile glass beads, the flask was thoroughly shaken for three hours. The fluid was then filtered through cotton to remove clumps, centrifuged and standardized in terms of bacilli in an average field of the oil immersion lens.

In the experiments on rabbits a different method of standardization was used. A small bit of growth on the surface of a glycerine bouillon culture was removed with a platinum tip, dried over calcium chloride and a determined weight of the organism carefully emulsified in a measured amount of 0.85% salt solution.

The amounts of these suspensions used for inoculation varied, as will be noted in the individual protocols.

SERIES I.

September 29, 1911. Ten guinea-pigs (1-10) varying in weight from 290 to 330 gm., were each sensitized by the intraperitoneal injection of 15 mgm. of tuberculo-protein dissolved in 1 ccm. of water. After 25 days, one of the animals (1) was tested for anaphylaxis and succumbed in acute shock within 4 minutes. None of the other treated animals were reinjected, inasmuch as experience had shown that this amount of protein almost invariably caused sensitization.

October 23, 1911. The other nine guinea-pigs, 2 to 10, together with nine non-sensitized normal guinea-pigs, 201 to 211, of the same weight, each received in the subcutaneous tissue of the left groin 0.2 ccm. of a suspension of Hα, which contained three bacilli in an average field of the oil immersion lens.

December 7. Guinea-pig 7, dead in cage. Weight 200 gm., loss of weight, 75 gm. The lymph glands in the left groin are small and show central plugs of caseation, but there is no local reaction in the subcutaneous tissue about them. The lungs are hyperæmic, and scattered through the parenchyma are many small gray tubercles. The spleen is swollen and studded with many tubercles, none of which are caseous. The other viscera show no tuberculous involvement.

December 11. Guinea-pig 2, found dead in cage. Weight 180 gm., loss of weight 65 gm. There is a large caseous abscess in the left groin, and the regional lymph nodes are swollen and caseating. The lungs are edematous and mottled with gray tubercles, 0.5 to 1.5 mm. in diameter. The spleen is enlarged and shows subcapsular tubercles. The other viscera are apparently uninvolved.

Guinea-pigs 3, 6 and 8, and controls 201, 204, 206 and 208, died on December 14 of an acute intercurrent infection. In all of these the lungs and the spleen showed the presence of tuberculosis and there was also an abscess in each at the site of inoculation. The other animals in this series were immediately killed and the cages cleaned and fumigated.

December 7. Guinea-pig 202, control animal, was etherized and the progress of the disease compared with that in guinea-pig 7. Weight 260 gm., loss of weight 20 gm. There is a small local abscess in the left groin. The spleen is enlarged and studded with gray tubercles. The other viscera are apparently normal.

December 11. Guinea-pig 209 etherized and the lesions compared with those found in sensitized guinea-pig 2. Weight 220 gm., loss of weight 15 gm. There is a local abscess in the left groin, with swelling of the regional lymph glands. The spleen is enlarged and shows many gray tubercles. The other viscera are apparently uninvolved.

Only four animals in Series I were really available for study, and for that reason, the same procedure was repeated in Series II.

SERIES II.

December 15. Guinea-pigs 12 to 23, inclusive, each received an injection of 15 mgm. of tuberculo-protein by the intraperitoneal route. Each of these animals was paired with a non-sensitized control animal (guinea-pigs 211 to 240) and on January 9 each received, in the subcutaneous tissues of the left groin, 0.2 ccm. of a suspension of Hα, which contained two bacilli in each 2½ fields of the oil immersion lens. Ten of the sensitized animals, together with the ten corresponding controls, were killed on the fifty-fifth day after infection and thereafter ten pairs were etherized on the seventieth and on the one hundred and fiftieth day, respectively, for a comparison of the lesions produced.

A.

Guinea-pigs 12 to 24, infected twenty-four days after the injection of the tuberculo-protein and guinea-pigs 211 to 221, control, non-sensitized animals, were etherized on March 6, fifty-five days after infection.

Guinea-pig 12. Well nourished, weight 270 gm., gain of weight 10 gm. There is a large caseous abscess in the left groin and the regional lymph glands are enlarged and softened. The spleen is swollen, firm and studded with gray tubercles, 1 to 2 mm. in diameter. The other viscera are uninvolved.

Guinea-pig 13. Emaciated, weight 200 gm., loss of weight 60 gm. There is a small caseous gland in the left inguinal region. The lungs are congested and show a few scattered gray tubercles. The spleen is enlarged, tense and studded with gray tubercles up to 2 mm. in diameter. The other viscera show no gross tuberculosis.

Guinea-pig 14. Emaciated, weight 210 gm., loss of weight 39 gm. The lymph glands in the left groin are necrotic. The lungs are congested and show fairly numerous gray tubercles throughout the parenchyma. The spleen is soft and dotted with numerous gray tubercles. There is no evident disease of the other viscera.

Guinea-pig 15. Well nourished, weight 260 gm. Weight unchanged since infection. The inguinal and the iliac lymph glands on the left side are small and on section show a central plug of caseation. The other viscera, except the spleen, appear normal. The spleen is slightly enlarged, firm, and scattered through it are many tubercles.

Guinea-pig 16. Well nourished, weight 250 gm., gain of weight 10 gm. There is a small caseating abscess in the left groin and the left inguinal lymph glands are swollen and softened. The lungs are pale, emphysematous and show many tubercles. The spleen is riddled with young tubercles.

Guinea-pig 17. Emaciated, weight 200 gm., loss of weight 65 gm. There is a large caseating abscess in the left groin, where the inguinal and the iliac glands are completely replaced by a fibrous sac with yellow caseous contents. The lungs are hyperæmic and show many small tubercles. The spleen contains many miliary tubercles. The other viscera appear normal.

Guinea-pig 18. Well nourished, weight 275 gm., gain of weight 25 gm. Careful examination shows tubercles only in the spleen, where they are numerous, gray in color, and 1 to 1.5 mm. in diameter.

Guinea-pig 19. Well nourished, weight 225 gms., loss of weight 30 gm. There is a fluctuating abscess in the left groin, the contents of which contain many tubercle bacilli. The regional lymph

glands are swollen and softened. The lungs are pale and collapsed and show many tubercles. The spleen is similarly involved. The other organs show no gross lesions.

Guinea-pig 20. Emaciated, weight 190 gm., loss of weight 38 gm. There is a large abscess in the left groin, and the regional lymph glands are swollen and caseating. The spleen is enlarged and mottled with gray tubercles. No other evidence of tuberculosis is found.

Guinea-pig 21. Emaciated, weight 210 gm., loss of weight 50 gm. The lymph glands in the left groin are caseous. The lungs are pink and studded with gray tubercles, 1 to 1.5 mm. in diameter. The spleen is swollen and shows many fresh tubercles. Otherwise the viscera appear normal.

Guinea-pig 22. Under nourished, weight 235 gm., loss of weight 25 gm. There is a large abscess in the left groin. The lungs and the spleen are studded with fresh tubercles; otherwise no evidence of tuberculosis is found.

Guinea-pig 23. Well nourished, weight 245 gm., gain of weight 15 gm. There is a small abscess in the left groin and the lymph glands in the left inguinal and iliac regions are fibrosed. No tubercles are seen in the viscera.

Control, non-sensitized guinea-pigs injected with the same dose of the same suspension on December 15, 1911, and etherized on March 6, 1912.

Guinea-pig 211. Well nourished, weight 290 gm., gain of weight 30 gm. There is no local abscess in the left groin but the deep inguinal glands show central caseation. The spleen is enlarged and mottled with tiny gray tubercles. No other evidence of disease is found.

Guinea-pig 212. Well nourished, weight 275 gm., gain of weight 12 gm. There is a small caseating abscess in the left groin, and the regional lymph glands are swollen, and have caseous centers. The spleen is enlarged and studded with gray tubercles, 1 to 1.5 mm. in diameter. The other viscera appear normal.

Guinea-pig 213. Under nourished, weight 240 gm., loss of weight 20 gm. There is a large caseating mass of glands in the left inguinal fossa. The lungs are congested and scattered through them are many miliary tubercles. The spleen is similarly affected. The other organs are uninvolved.

Guinea-pig 214. Under nourished. Weight 210 gm., loss of weight 25 gm. There is a large caseating abscess in the left groin and the regional lymph glands are enlarged and softened. The lungs and the spleen show numerous gray tubercles.

Guinea pig 215. Emaciated, weight 119 gm., loss of weight 40 gm. There is an abscess in the left groin and the regional inguinal and iliac lymph nodes are soft and necrotic. All the viscera appear normal, except the spleen, which is mottled with gray tubercles.

Guinea-pig 216. Emaciated, weight 185 gm., loss of weight 45 gm. There is no reaction at the site of injection, but there is a central caseating plug in the center of one of the left inguinal lymph nodes. The spleen shows numerous gray tubercles. Otherwise no tuberculosis is manifest.

Guinea-pig 217. Emaciated, weight 200 gm., loss of weight 40 gm. There is a caseating abscess in the left inguinal fossa and the spleen shows numerous miliary tubercles. There is no tuberculous involvement of the other organs.

Guinea-pig 218. Under nourished, weight 240 gm., loss of weight 15 gm. There is no local abscess in the groin, but the adjacent lymph glands have caseating centers. There are numerous small tubercles in the spleen.

Guinea-pig 219. Well nourished, weight 245 gm. In the left inguinal region the glands are softened and have central caseating plugs. No other evidence of tuberculosis found.

Guinea-pig 220. Well nourished, weight 255 gm., gain of weight 15 gm. There are two small caseating lymph nodes in the left groin. The spleen shows a few gray tubercles scattered through its pulp. The other viscera appear normal.

Guinea-pig 221. Well nourished, weight 270 gm., gain of weight 15 gm. The inguinal and the iliac lymph glands on the left side are necrotic. The spleen is mottled with gray tubercles. The other viscera appear normal.

TABLE I

Guinea-pig No.	Preliminary treatment	Duration of life after infection	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
	Tuberculo-protein	*Days*						
7	15 mgm.	* 45	+	—	+	—	+	
2	do.	* 49	+	—	+	—	+	
3	do.	* 52	+	—	+	—	+	Intercurrent infection
6	do.	* 52	+	—	+	—	+	
8	do.	* 52	+	—	+	—	+	
202	None	† 45	—	—	+	—	+	
209	do.	† 49	—	—	+	—	+	
12	15 mgm.	† 55	—	—	+	—	+	Well nourished
13	do.	† 55	+	—	+	—	+	
14	do.	† 55	+	—	+	—	+	
15	do.	† 55	—	—	+	—	+	Well nourished
16	do.	† 55	+	—	+	—	+	Well nourished
17	do.	† 55	+	—	+	—	+	
18	do.	† 55	—	—	+	—	—	Well nourished
19	do.	† 55	+	—	+	—	+	
20	do.	† 55	—	—	+	—	+	
21	do.	† 55	+	—	+	—	+	
22	do.	† 55	+	—	+	—	+	
23	do.	† 55	—	—	—	—	+	Well nourished
211	None	† 55	—	—	+	—	+	Well nourished
212	do.	† 55	—	—	+	—	+	Well nourished
213	do.	† 55	—	—	+	—	+	
214	do.	† 55	+	—	+	—	+	
215	do.	† 55	—	—	+	—	+	
216	do.	† 55	—	—	+	—	+	
217	do.	† 55	—	—	+	—	+	
218	do.	† 55	—	—	+	—	+	Well nourished
219	do.	† 55	—	—	—	—	+	
220	do.	† 55	—	—	+	—	+	Well nourished
221	do.	† 55	—	—	+	—	+	Well nourished

* Died. † Etherized.

If it be borne in mind that in this series of experiments each animal received exactly the same dose of bacilli, injected with identical technique and in the same region of the body; that each was kept under the same conditions for the same length of time before it was killed, certain differences are strikingly apparent. Of the animals sensitized before infection, six showed involvement of the lungs and nine showed tubercles in the spleen, whereas of the non-sensitized control guinea-pigs, pulmonary involvement was present in only one and the spleen was diseased in nine. It seems evident then that, even aside from normal individual differences in resistance to infection, there was greater immunity to tuberculosis in the non-sensitized than in the treated animals. Apparently sensitization with our tuberculo-protein had lessened the normal resisting power to tuberculous infection.

B.

March 21. Sensitized guinea-pigs 25 to 35, inclusive, etherized on the seventieth day after infection.

Guinea-pig 25. Emaciated, weight 210 gm., loss of weight 40 gm. There is a caseating abscess in the left groin, and the adjacent lymph glands are necrotic. The spleen shows numerous gray tubercles, one or two of which have become caseous. The lungs are studded throughout with small yellow tubercles. The other viscera appear normal.

Guinea-pig 26. Emaciated, weight 200 gm., loss of weight 30 gm. There is a small caseous abscess in the left groin and the adjacent lymph glands are swollen and soft. The lungs and kidneys are negative but the spleen shows numerous tiny gray tubercles.

Guinea-pig 27. Well nourished, weight 295 gm., gain of weight 40 gm. No abscess is found in the groin but the left inguinal lymph glands are necrotic. There are no signs of tuberculosis in the viscera.

Guinea-pig 28. There is a large soft abscess in the left inguinal region, and a few yellow tubercles, 3 mm. in diameter in the lungs and in the spleen.

Guinea-pig 29. Well nourished, weight 280 gm., gain of weight 20 gm. There is a large abscess in the left inguinal fossa and the regional lymph glands are necrotic. A few yellow tubercles, 3 mm. in diameter, are seen in the lungs and spleen.

Guinea-pig 30. Emaciated, weight 230 gm., loss of weight 20 gm. There is no abscess in the groin but the inguinal lymph glands are caseous. The lungs are congested and edematous, but there is no macroscopic tuberculosis. The spleen shows numerous gray and yellow tubercles.

Guinea-pig 31. Well nourished, weight 300 gm., gain of weight 40 gm. There is a small caseous abscess in the left inguinal region and the lymph nodes are necrotic. A few yellow tubercles are seen in the lungs and in the spleen.

Guinea-pig 32. Well nourished, weight 300 gm., gain of weight 35 gm. There is a small caseating abscess in the left groin and the regional lymph glands are caseous. Aside from numerous gray tubercles in the spleen, there is no evident tuberculosis.

Guinea-pig 33. Emaciated, weight 205 gm., loss of weight 30 gm. The left inguinal lymph nodes are caseous. There is an acute bronchitis and peribronchitis, but no tubercles are seen in the lungs. The spleen is small, but riddled with gray and yellow tubercles. There is evident enlargement of the mesenteric lymph glands.

Guinea-pig 34. Emaciated, weight 200 gm., loss of weight 25 gm. There are enlarged caseating lymph nodes in the left groin. The lungs show numerous caseating tubercles and a few which have undergone fibrosis. There are also numerous yellow tubercles in the spleen.

Guinea-pig 35. Well nourished, weight 230 gm., loss of weight 10 gm. The lymph glands in the left inguinal region are large and necrotic. Numerous gray and yellow tubercles are seen throughout the lungs and the spleen. The other viscera appear normal.

Control non-sensitized guinea-pigs, 222 to 232, etherized on the seventieth day after infection, for a comparison of the lesions with those found in the foregoing sensitized animals.

Guinea-pig 222. Well nourished, weight 290 gm., gain of weight 30 gm. There is a small abscess in the left groin and numerous tiny gray tubercles are seen in the spleen. The other viscera are uninvolved.

Guinea-pig 223. Well nourished, weight 310 gm., gain of weight 40 gm. There is a caseating abscess in the left groin but there is no evident tuberculosis of any of the viscera.

Guinea-pig 224. Well nourished, weight 315 gm., gain of weight 45 gm. The lymph glands in the left groin are caseous Numerous gray tubercles are seen throughout the lungs and the spleen is mottled with gray and yellow nodules.

Guinea-pig 225. Under nourished, weight 240 gm., loss of weight 30 gm. There is no abscess in the groin, but the inguinal and the iliac lymph glands show central plugs of caseation. There are numerous miliary tubercles scattered throughout the lungs and the spleen is mottled with gray and yellow tubercles.

Guinea-pig 226. Emaciated, weight 200 gm., loss of weight 40 gm. There is a small caseating abscess in the left groin, with necrotic regional lymph nodes. There are numerous gray tubercles throughout the lungs and the spleen, several of which are undergoing softening.

Guinea-pig 227. Emaciated, weight 225 gm., loss of weight 30 gm. The inguinal and the iliac lymph glands are necrotic. There are no tubercles to be seen in the lungs or in any of the viscera except in the spleen, in which a few large yellow tubercles, 2.5 mm. in diameter, are seen.

Guinea-pig 228. Emaciated, weight 190 gm., loss of weight 40 gm. There are necrotic caseating lymph nodes in the left groin and the spleen is distorted by numerous yellow, softened tubercles. Otherwise the viscera are uninvolved.

Guinea-pig 229. Emaciated, weight 205 gm., loss of weight 42 gm. There is a small caseating lymph gland in the left groin, with infiltration of the adjacent muscles. The lungs show an acute broncho-pneumonia, and peribronchitis. The spleen is small and studded with gray tubercles. The mesenteric lymph nodes are swollen but are not necrotic.

Guinea-pig 230. Under nourished, weight 205 gm., loss of weight 30 gm. There is no local reaction in the left groin, except central caseation of the inguinal lymph glands. There are numerous gray, and a few yellow tubercles throughout the lungs, and the spleen is riddled with gray tubercles, 1 mm. in diameter.

Guinea-pig 231. Emaciated, weight 200 gm., loss of weight 25 gm. The left inguinal lymph nodes are necrotic and there is a caseating abscess involving the deep structures of the thigh. The lungs are dotted with large tubercles, 0.5 to 1.5 mm. in diameter, which show central caseation. The spleen is enlarged and studded with yellow tubercles. The mesenteric lymph nodes are swollen.

Guinea-pig 232. Emaciated, weight 195 gm., loss of weight 35 gm. There are central caseous plugs in the left inguinal and iliac lymph glands. There is no tuberculosis evident in any of the viscera except the spleen, which shows numerous small yellow tubercles.

TABLE II

Guinea-pig No.	Preliminary treatment	Duration of life after infection	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
	Tuberculo-protein	*Days*						
25	15 mgm.	† 70	+	−	+	−	+	
26	do.	† 70	−	−	+	−	+	
27	do.	† 70	−	−	−	−	+	Well nourished
28	do.	† 70	+	−	+	−	+	Well nourished
29	do.	† 70	+	−	+	−	+	Well nourished
30	do.	† 70	−	−	+	−	+	
31	do.	† 70	+	−	+	−	+	Well nourished
32	do.	† 70	−	−	+	−	+	Well nourished
33	do.	† 70	−	−	+	−	+	
34	do.	† 70	−	−	+	−	+	
35	do.	† 70	+	−	+	−	+	Well nourished
222	None	† 70	−	−	+	−	+	Well nourished
223	do.	† 70	−	−	−	−	+	Well nourished
224	do.	† 70	+	−	+	−	+	Well nourished
225	do.	† 70	+	−	+	−	+	
226	do.	† 70	+	−	+	−	+	
227	do.	† 70	−	−	+	−	+	
228	do.	† 70	−	−	+	−	+	
229	do.	† 70	−	−	+	−	+	
230	do.	† 70	+	−	+	−	+	
231	do.	† 70	+	−	+	−	+	
232	do.	† 70	−	−	+	−	+	

† Etherized.

C.

Sensitized guinea-pigs 60 to 65 and 72 to 77, inclusive, infected January 9 and control non-sensitized guinea-pigs 260 to 275, inclusive, in which the disease had existed the same length of time, were etherized one hundred and fifty-seven days later, on June 15.

Guinea-pig 60. Well nourished, weight 230 gm., gain of weight 10 gm. There is a small abscess in the left groin and the associated inguinal lymph glands are necrotic. The spleen is riddled with gray tubercles. The other viscera are apparently uninvolved.

Guinea-pig 61. Emaciated, weight 195 gm., loss of weight 30 gm. There is a large caseating abscess in the left inguinal fossa

and the regional lymph nodes are softened. The lungs are studded with numerous yellow tubercles, about many of which there is a zone of fibrous tissue but there is no cavity formation. The spleen is enlarged and distorted by caseating tubercles. There are a few gray tubercles in the cortex of each kidney.

Guinea-pig 62. Emaciated, weight 200 gm., loss of weight 40 gm. The lungs are voluminous and throughout them there are numerous softened yellow tubercles. There are many miliary tubercles in the spleen and in the kidneys.

Guinea-pig 63. Emaciated, weight 200 gm., loss of weight 35 gm. There is a necrotic abscess in the left groin and the neighboring lymph glands are necrotic. The lungs and the spleen show very numerous gray and yellow tubercles. None of the other viscera are diseased.

Guinea-pig 64. Emaciated, weight 185 gm., loss of weight 50 gm. There is a fluctuating abscess in the left inguinal fossa and the inguinal and iliac lymph glands on this side are caseous. The lungs show numerous caseating tubercles and two small cavities. The spleen is much enlarged and studded with gray and yellow tubercles.

Guinea-pig 65. Emaciated, weight 220 gm., loss of weight 40 gm. The lungs are voluminous and show small areas of consolidation, with many tubercles. The spleen is enlarged and throughout its parenchyma are numerous small tubercles.

Guinea-pig 72. Well nourished, weight 220 gm., loss of weight 15 gm. There is a small abscess in the left groin, and central plugs of caseation are seen in the regional lymph glands. The spleen shows numerous gray and yellow tubercles. Otherwise there is no evidence of the disease in the viscera.

Guinea-pig 73. Under nourished, weight 240 gm., loss of weight 10 gm. The inguinal and the iliac lymph nodes are softened and necrotic. The lungs and the other viscera, with the exception of the spleen, show no tuberculous involvement. The spleen is much enlarged, firm, and scattered through it are very numerous yellow and gray tubercles.

Guinea-pig 74. Well nourished, weight 250 gm. No change in weight since the time of inoculation. The inguinal and the iliac lymph nodes on the left side are small, fibrous and show central necrotic plugs. The spleen is enlarged and shows fairly numerous yellow and gray tubercles. There are no tubercles seen in the lungs or in the other viscera.

Guinea-pig 75. Emaciated, weight 205 gm., loss of weight 43 gm. There is a small abscess in the left groin and the associated lymph nodes are necrotic. There are a few large yellow tubercles and numerous miliary tubercles scattered through the lungs and the spleen.

Guinea-pig 76. Well nourished, weight 235 gm., gain of weight 5 gm. The inguinal and the iliac lymph nodes show central necrosis. The spleen is enlarged and in its parenchyma numerous small yellow and gray tubercles are visible. No tuberculous involvement of the other internal organs is seen.

Guinea-pig 77. Emaciated, weight 211 gm., loss of weight 19 gm. The left inguinal and iliac lymph nodes are completely necrotic. The spleen is much enlarged and distorted by numerous yellow tubercles. The other viscera, aside from cloudy swelling, appear normal.

CONTROLS.

Guinea-pig 260. Emaciated, weight 204 gm., loss of weight 28 gm. The lymph nodes in the left inguinal fossa are caseous. The spleen is enlarged, firm, and mottled with large gray tubercles. The other viscera are uninvolved in the process.

Guinea-pig 261. Under nourished, weight 230 gm., loss of weight 12 gm. There is a suppurating abscess in the left inguinal fossa, where the glands are necrotic and softened. There is no evidence of tuberculosis except in the spleen, where numerous gray tubercles are scattered through the parenchyma.

Guinea-pig 262. Emaciated, weight 208 gm., loss of weight 22 gm. There is no abscess in the left groin but there is a central plug of caseation in one of the left inguinal lymph glands. The spleen is the only organ in which evident tuberculosis is manifest, and it is distorted by many yellow and gray tubercles.

Guinea-pig 263. The left inguinal and iliac lymph glands show fibrosis and central caseation. There is no tuberculous involvement of any of the viscera except the spleen, throughout which many caseating tubercles are seen.

Guinea-pig 264. Well nourished, weight 255 gm., gain of weight 15 gm. The inguinal and the iliac lymph nodes on the left are partially necrotic. The spleen is enlarged and scattered through it are many fresh and caseous tubercles.

Guinea-pig 265. Emaciated, weight 22 gm., loss of weight 38 gm. The left inguinal anl iliac lymph glands are swollen and partially necrotic; the spleen is enlarged and firm, and shows many gray tubercles.

Guinea-pig 270. Well nourished, weight 270 gm., gain of weight 20 gm. There is a small caseating abscess in the left inguinal region and the regional lymph nodes show central necrosis. The spleen and the lungs show fairly numerous caseating tubercles.

Guinea-pig 271. Under nourished, weight 230 gm., loss of weight 18 gm. There is a necrotic plug in one of the left inguinal lymph nodes. The spleen is enlarged and distorted by numerous yellow tubercles. No other tuberculous involvement found.

Guinea-pig 272. Well nourished, weight 260 gm., gain of weight 5 gm. Aside from a small abscess in the left iliac region and numerous gray tubercles throughout the spleen, the viscera are normal.

Guinea-pig 273. Emaciated, weight 212 gm., loss of weight 38 gm. There are numerous tubercles scattered throughout the spleen; otherwise no evidence of tuberculosis is found.

Guinea-pig 274. Well nourished, weight 255 gm., gain of weight 3 gm. There is a small caseating abscess in the left groin, with necrosis of the associated lymph glands. No visceral tuberculosis is found except in the spleen, where there are many gray and yellow tubercles.

Guinea-pig 275. Emaciated, weight 215 gm., loss of weight 25 gm. There is necrosis of the iliac lymph nodes and a few gray tubercles are scattered throughout the lungs. The spleen is enlarged, firm, and distorted by numerous large caseating tubercles.

TABLE III

Guinea-pig No.	Preliminary treatment	Duration of life after inoculation	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
	Tuberculo-protein	*Days*						
60	15 mgm.	† 157	−	−	+	−	+	Well nourished
61	do.	† 157	+	−	+	+	+	
62	do.	† 157	+	−	+	−	+	
63	do.	† 157	+	−	+	+	+	
64	do.	† 157	+	−	+	−	+	
65	do.	† 157	+	−	+	−	+	
72	do.	† 157	−	−	+	−	+	Well nourished
73	do.	† 157	−	−	+	−	+	Well nourished
74	do.	† 157	−	−	+	−	+	Well nourished
75	do.	† 157	+	−	+	−	+	
76	do.	† 157	−	−	+	−	+	Well nourished
77	do.	† 157	−	−	+	−	+	
261	None	† 157	−	−	+	−	+	
262	do.	† 157	−	−	+	−	+	
263	do.	† 157	−	−	+	−	+	
264	do.	† 157	−	−	+	−	+	Well nourished
265	do.	† 157	−	−	+	−	+	Well nourished
270	do.	† 157	+	−	+	−	+	Well nourished
271	do.	† 157	−	−	+	−	+	
272	do.	† 157	−	−	+	−	+	Well nourished
273	do.	† 157	−	−	+	−	+	
274	do.	† 157	−	−	+	−	+	Well nourished
275	do.	† 157	+	−	+	−	+	

† Etherized.

The evidence furnished by this series of experiments also was definite, and it was quite clear that sensitization with a tuberculo-protein had definitely diminished the resistance of the animals to infection with living bacilli of the human type. Mindful of the fact that tuberculous animals, though immune to reinfection with small numbers of bacilli, are less resistant to reinfection with larger numbers of the organisms, a second series of sensitized guinea-pigs, with a parallel series of control animals, were infected with smaller doses of the strain of tubercle bacilli used in the preceding experiments.

SERIES III.

January 10, 1912. Ten guinea-pigs, 81-90, were sensitized by the intraperitoneal injection of 15 mgm. of tuberculo-protein; twenty-four days later, on February 3, these animals, together with ten non-sensitized guinea-pigs, received subcutaneously, in the tissues of the left groin, 0.1 ccm. of a suspension of H_{α}, which contained one organism in every two fields of the oil immersion lens. Eighty-five days after inoculation, on April 29, all twenty animals were etherized, sectioned, and the lesions compared.

SENSITIZED GUINEA-PIGS 81-90.

Guinea-pig 81. Emaciated, weight 210 gm., loss of weight 43 gm. There is a small caseous abscess in the left inguinal region, with necrosis of the associated lymph glands. The lungs show a most striking picture; they are hyperemic and mottled with large yellow plaques of caseation. The mediastinal lymph glands are large and firm. The spleen is not enlarged and shows relatively few gray tubercles. The other viscera are uninvolved.

Guinea-pig 82. Emaciated, weight 205 gm., loss of weight 38 gm. There are enlarged inguinal and iliac lymph glands on the left side that show central caseation. The lungs are pale and translucent, and dotted with yellow tubercles. The spleen is enormously enlarged, the pulp increased, and studded with yellow tubercles. The mesenteric lymph nodes are swollen.

Guinea-pig 83. Fairly well nourished, weight 240 gm., loss of weight 15 gm. The glands in the left groin are necrotic and there is infiltration of the adjacent muscle. The lungs show numerous gray and yellow tubercles. The spleen is small and studded with gray tubercles.

Guinea-pig 84. Under nourished, weight 205 gm., loss of weight 23 gm. There is a large caseating abscess in the left groin, with caseous adjacent lymph glands. There are a few yellow tubercles in the spleen. Otherwise the internal organs appear normal.

Guinea-pig 85. Emaciated, weight 203 gm., loss of weight 20 gm. There is a small caseating abscess in the left groin, with necrosis of the iliac lymph glands. Except for large yellow caseous tubercles throughout the spleen, the viscera are uninvolved.

Guinea-pig 86. Well nourished, weight 310 gm., gain of weight 50 gm. There is beginning caseation of the lymph nodes and a necrotic abscess in the left inguinal fossa. There are numerous gray tubercles throughout the lungs and the spleen.

Guinea-pig 87. Well nourished, gain of weight 15 gm. There is a large abscess in the left groin, with coagulation necrosis of the inguinal and of the iliac lymph nodes. There are a few yellow and gray tubercles in the spleen, and marked congestion of the other viscera.

Guinea-pig 88. Emaciated, loss of weight 40 gm. There is no macroscopic tuberculosis, except in the left inguinal lymph glands, which are necrotic, and in the spleen, which is mottled with yellow and gray tubercles.

Guinea-pig 89. Well nourished, weight 250 gm. Weight stationary since injection. The left inguinal and iliac lymph glands are slightly enlarged and fibrous. There are numerous gray tubercles throughout the parenchyma of the spleen. Otherwise the viscera appear normal.

Guinea-pig 90. Well nourished, weight 290 gm., gain of weight 18 gm. A small caseating abscess and several large caseating lymph glands are seen in the left inguinal fossa. There are numerous tubercles scattered through the spleen.

CONTROL GUINEA-PIGS 280-290.

Guinea-pig 280. Well nourished, weight 290 gm., gain of weight 20 gm. There is a small fluctuating abscess in the left groin and a marked swelling of the adjacent lymph glands, some of which show central caseation. All of the viscera appear normal except the spleen, which is mottled with numerous gray tubercles.

Guinea-pig 281. Well nourished, weight 300 gm., gain of weight 45 gm. (pregnant). There is a small caseating abscess in the left groin and the adjacent lymph glands are necrotic. The lungs show no evidence of tuberculosis. The spleen is some what enlarged and distorted by numerous gray tubercles.

Guinea-pig 282. Well nourished, weight 260 gm., gain of weight 12 gm. The lymph glands in the left inguinal fossa are caseous and there are a few gray tubercles scattered throughout the spleen. Otherwise no evidence of tuberculous involvement is apparent.

Guinea-pig 283. Well nourished, weight 275 gm., unchanged since infection. The inguinal and the iliac lymph nodes on the left are fibrous and show central caseation. There are numerous gray tubercles in the parenchyma of the spleen.

Guinea-pig 284. Well nourished, weight 285 gm., gain of weight 26 gm. (pregnant). There is a small suppurating abscess in the left groin. The adjacent lymph nodes are necrotic and there are numerous yellow and a few gray tubercles in the spleen.

Guinea-pig 285. Well nourished, weight 285 gm., gain of weight 12 gm. The left inguinal and iliac lymph glands are small and show central necrosis. A few fresh gray tubercles are seen in the lungs and numerous older tubercles are scattered throughout the spleen.

Guinea-pig 286. Emaciated, weight 245 gm., loss of weight 7 gm. There is a small abscess in the left groin and the adjacent lymph glands are swollen and infiltrated. The spleen is enlarged, firm and mottled with gray tubercles.

Guinea-pig 287. Well nourished, weight 272 gm., gain of weight 14 gm. There is no abscess in the left groin, but the inguinal and the iliac lymph nodes are softened and necrotic. The spleen is slightly enlarged, very firm and throughout it are numerous yellow tubercles.

Guinea-pig 288. Weight 250 gm., loss of weight 18 gm. The inguinal and the iliac lymph nodes are softened and caseous. Except for numerous gray tubercles throughout the spleen, the other internal organs appear normal.

Guinea-pig 289. Emaciated, weight 228 gm., loss of weight 39 gm. The inguinal lymph nodes on the left side show central necrosis and there are numerous yellow tubercles in the spleen.

Guinea-pig 290. Well nourished, weight 265 gm., gain of weight 8 gm. There is a small caseating abscess in the left groin and the regional lymph glands are fibrosed. No evidence of tuberculosis is visible in the viscera.

TABLE IV

Guinea-pig No.	Preliminary treatment	Duration of life after infection	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
	Tuberculo-protein	*Days*						
81	15 mgm.	† 85	+	—	+	—	+	
82	do.	† 85	+	—	+	—	+	
83	do.	† 85	+	—	+	—	+	Well nourished
84	do.	† 85	—	—	+	—	+	
85	do.	† 85	—	—	+	—	+	
86	do.	† 85	+	—	+	—	+	Well nourished
87	do.	† 85	—	—	+	—	+	Well nourished
88	do.	† 85	—	—	+	—	+	
89	do.	† 85	—	—	+	—	+	Well nourished
90	do.	† 85	—	—	+	—	+	Well nourished
280	None	† 85	—	—	+	—	+	Well nourished
281	do.	† 85	—	—	+	—	+	Pregnant
282	do.	† 85	—	—	+	—	+	Well nourished
283	do.	† 85	—	—	+	—	+	Pregnant
284	do.	† 85	—	—	+	—	+	Well nourished
285	do.	† 85	+	—	+	—	+	Well nourished
286	do.	† 85	—	—	+	—	+	
287	do.	† 85	—	—	+	—	+	Well nourished
288	do.	† 85	—	—	+	—	+	
289	do.	† 85	—	—	+	—	+	
290	do.	† 85	—	—	—	—	+	Well nourished

† Etherized.

The findings in the experiments last cited are a confirmation of those already noted. Although the infecting doses of tubercle bacilli were small the already sensitized animals showed more extensive disease than did the non-sensitized controls. In four of the former the disease involved the lungs, whereas in only one of the latter did the disease spread beyond the spleen.

SERIES IV.

To determine the influence of sensitization produced by the repeated injections of small amounts of tuberculo-protein, each of ten guinea-pigs (95 to 105) received twenty-two intraperitoneal injections of 2 mgm. of tuberculo-protein at intervals of two days. These animals were caged with control guinea-pigs 293 to 303, and all were inoculated with 0.1 ccm. of a suspension of Ha in salt solution, which contained one bacillus in an average field of the oil immersion lens. They were etherized on the seventy-fifth day after inoculation, and a comparative study made of the resultant lesions. Three of the animals, two sensitized and one control, were not available for this experiment, having died from intercurrent colitis.

Sensitized Guinea-Pigs.

Guinea-pig 95. Well nourished, weight 240 gm., loss of weight 10 gm. There is a small caseating abscess and several large caseating glands in the left inguinal fossa. The spleen is studded with gray tubercles. The other viscera are uninvolved.

Guinea-pig 96. Well nourished, weight 225 gm., loss of weight 12 gm. There is a small abscess in the left groin and the regional lymph glands are necrotic. The spleen shows numerous gray tubercles. No other manifestations of tuberculosis found.

Guinea-pig 97. Well nourished, weight 235 gm., gain of weight 5 gm. There is a small fluctuating abscess in the left groin, with fibrosis of the adjacent lymph glands and there are numerous tubercles scattered through the spleen. The other viscera are normal.

Guinea-pig 98. Under nourished, weight 210 gm., loss of weight 10 gm. The inguinal and the iliac lymph nodes on the left side show central plugs of caseation. There are numerous gray tubercles scattered through the parenchyma of the spleen.

Guinea-pig 99. Well nourished, weight 250 gm., gain of weight 10 gm. There is a small caseating abscess in the left groin, with necrosis of the adjacent lymph glands. The spleen is enlarged and mottled with gray tubercles, 0.5 to 2 mm. in diameter.

Guinea-pig 100. Well nourished, weight 260 gm., loss of weight 15 gm. The lymph nodes in the left inguinal fossa are necrotic. The spleen is enlarged, firm and studded with fresh tubercles.

Guinea-pig 101. Well nourished, weight 235 gm., gain of weight 6 gm. There is a large caseating abscess in the left groin with necrosis of the adjacent lymph glands. The lungs and spleen are riddled with numerous gray tubercles and a few small caseating nodules.

Guinea-pig 103. Well nourished, weight 265 gm., gain of weight 22 gm. (pregnant). Aside from caseation of the left inguinal and iliac lymph nodes there is no evidence of tuberculosis.

Control Non-Sensitized Guinea-Pigs.

Guinea-pig 293. Well nourished, weight 265 gm., gain of weight 15 gm. There is a small caseating abscess in the left groin with necrosis of the adjacent lymph glands. The spleen is enlarged and distorted by numerous tubercles.

Guinea-pig 294. Emaciated, weight 222 gm., loss of weight 18 gm. There is a small fluctuating abscess in the left groin with central necrosis of the adjacent lymph nodes. The spleen is riddled with numerous gray tubercles. The other viscera appear normal.

Guinea-pig 295. Well nourished, weight 275 gm., gain of weight 35 gm. (pregnant). The left inguinal lymph nodes show central plugs of caseation and the spleen is mottled with fresh gray tubercles, 0.4 to 2 mm. in diameter.

Guinea-pig 296. Well nourished, weight 245 gm., gain of weight 20 gm. There is fibrosis of the left inguinal lymph nodes and there are numerous gray tubercles throughout the parenchyma of the spleen.

Guinea-pig 297. Well nourished, weight 250 gm., gain of weight 15 gm. There is no abscess at the site of inoculation but the left inguinal lymph nodes are necrotic and soft. The spleen is not enlarged, but is studded with fresh gray and a few larger yellow tubercles.

Guinea-pig 299. Under nourished, weight 230 gm., loss of weight 15 gm. There is a small caseating abscess in the left groin, with necrosis of the associated lymph nodes. The lungs and spleen show many miliary tubercles.

Guinea-pig 300. Emaciated, weight 212 gm., loss of weight 19 gm. There is a small caseating abscess in the left inguinal fossa with fibrosis of the adjacent lymph nodes. There are numerous gray tubercles in the lungs and in the spleen.

Guinea-pig 302. Well nourished, weight 245 gm., gain of weight 12 gm. There is a large fluctuating abscess in the left groin and the regional lymph nodes are completely necrotic. Otherwise, no evidence of tuberculosis is found.

Guinea-pig 303. Well nourished, weight 300 gm., gain of weight 45 gm. (pregnant). There is a caseating abscess in the left inguinal fossa and the associated iliac lymph nodes show central caseation. There is no macroscopic tuberculosis of the internal organs.

TABLE V

Guinea-pig No.	Preliminary treatment	Duration of life after infection	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
	Tuberculo-protein	*Days*						
95	44 mgm.	† 75	—	—	+	—	+	Well nourished
96	do.	† 75	—	—	+	—	+	Well nourished
97	do.	† 75	—	—	+	—	+	Well nourished
98	do.	† 75	—	—	+	—	+	
99	do.	† 75	—	—	+	—	+	Well nourished
100	do.	† 75	—	—	+	—	+	Well nourished
101	do.	† 75	+	—	+	—	+	Well nourished
103	do.	† 75	—	—	—	—	+	Pregnant
293	None	† 75	—	—	+	—	+	Well nourished
294	do.	† 75	—	—	+	—	+	
295	do.	† 75	—	—	+	—	+	Pregnant
296	do.	† 75	—	—	+	—	+	Well nourished
297	do.	† 75	—	—	+	—	+	Well nourished
299	do.	† 75	+	—	+	—	+	
300	do.	† 75	+	—	+	—	+	
302	do.	† 75	—	—	—	—	+	
303	do.	† 75	—	—	—	—	+	Well nourished

† Etherized.

In this experiment very little difference is to be noted in the extent of the disease in the sensitized and in the non-sensitized animals. In seven of the hypersensitive animals the spleen was involved; in only one were the lungs diseased and in one the infection remained strictly localized, whereas in the control, non-sensitized animals, in five the disease did not spread beyond the spleen, in two the lungs were involved and in two there was a localization of the process in the glands draining the site of inoculation. In short, the resistance of the animals that were sensitized was unchanged, or perhaps slightly increased.

Thus far, for the sake of completeness, the detailed findings in each set of experiments have been recorded; but for the sake of brevity, in the following experiments, details will be given only when omission of them would fail to bring out the salient points of the work.

Influence of the Refractory State Upon Infection.

SERIES V.

April 25, 1912. Five guinea-pigs, 114 to 118, inclusive, twenty-three days after the intraperitoneal injection of 14 mgm. of tuberculo-protein, were given a sublethal intravenous injection of 8 mgm. of the same preparation. Within two to four hours after the administration of the intoxicating dose, and while they still showed the symptoms of anaphylactic shock, these animals, together with five untreated non-sensitized controls (guinea-pigs 309 to 315) were each given 0.15 ccm. of a salt solution suspension of Ha, which contained two bacilli in every three fields of the oil immersion lens. Seventy-three days later (June 7) all of these animals were etherized and examined.

In all five of the intoxicated animals, the lungs and the spleen were involved in an acute miliary tuberculosis, and many of the lesions showed beginning caseation, whereas in only two of the controls had the disease invaded the lungs.

These findings are in accord with those of Krause, that refractory animals are less resistant to infection than are sensitized or non-sensitized animals. The lowering of resistance by shock, however, is not entirely specific, for while in this condition several other guinea pigs (118 to 122) succumbed to doses of virulent typhoid bacilli, which were not lethal, to untreated non-sensitized control animals.

To Test the Influence of Inherited Hypersensitiveness to a Tuberculo-Protein upon Infection with Bacillus Tuberculosis.

SERIES VI.

Twelve guinea-pigs, from twenty to forty days old, varying in weight from 105 to 190 gm. the offspring of actively sensitized mothers, and twelve guinea-pigs of the same age and about the same weight, born of non-sensitized, normal females, were used in this series.

A.

February 14, 1912. Five guinea-pigs with inherited hypersensitiveness to tuberculo-protein, together with seven normal young guinea-pigs, were injected into the subcutaneous tissues of the left groin, with 0.5 ccm. of a suspension of Ha in salt solution, which contained one bacillus in each field of the oil immersion lens.

On May 1, seventy-five days later, these animals were etherized, sectioned, and the lesions compared.

In three of the animals with inherited hypersensitiveness, there was, in addition to caseation at the site of inoculation, miliary tuberculosis of the lungs and spleen, whereas in the controls, the disease had involved no internal organ except the spleen. In two of the animals with inherited hypersensitiveness, and in two of the controls, there was a small abscess in the left inguinal region, with caseation of the regional lymph glands and numerous gray tubercles in the spleen.

B.

April 3. Seven guinea-pigs with inherited hypersensitiveness to tuberculo-protein and seven normal young guinea-pigs, were each given a subcutaneous injection into the left groin of the same amount of tubercle bacilli as was administered to the animals in Series A. They were all etherized on June 17 and the lesions compared.

In four of the sensitive animals, there was extensive tuberculosis of the lungs and spleen, with beginning caseation of the lesions, whereas the corresponding control animals showed caseation of the inguinal and iliac lymph glands and gray tubercles throughout the spleen, but no involvement of the lungs. In three of the sensitive guinea-pigs there was no further advance of the process than in the corresponding controls.

In this series, inherited hypersensitiveness to our tuberculo-protein brought about a diminution in the resisting power of the animals to infection by tubercle bacilli, just as in many instances the active sensitization did in the experiments already cited.

The diminished resistance to tuberculosis shown by the animals with inherited allergy, offers a possible explanation for the increased susceptibility to infection of the offspring of tuberculous mothers; and although it is unwise to hazard

speculation as to the cause of the great incidence of tuberculosis among the children of infected parents, still, in a certain small proportion of the cases, a similar mechanism may play some rôle.

A study of the resistance of animals in the preanaphylactic state to infection with tubercle bacilli cannot now be recorded, inasmuch as the animals in this series became infected with an acute intercurrent entero-colitis and were not available for study.

Hypersensitiveness to a Tuberculo-Protein and Infection with Bacillus Tuberculosis.

Rabbit Experiments.

Inasmuch as rabbits are relatively insusceptible to infection with the human type of bacillus tuberculosis, developing a slow chronic disease lasting months and unattended by a period of dyspnea, it was of interest to note if the course of the disease produced in them could be essentially modified by sensitization with a tuberculo-protein. In the following series of animals, it will be seen that some were treated with one large dose of the protein, others received several smaller doses at three-day intervals, and all were inoculated with tubercle bacilli about twenty days after the intraperitoneal sensitizing dose. For each sensitized animal, a control, untreated, of about equal weight and of the same age, sex and color, was used. All were caged together and kept under as nearly identical conditions as possible. In all instances, the suspensions of tubercle bacilli were prepared as already described, and the same substance was used to bring about the hypersensitive state.

December 14, 1911. Rabbit 5, white female, weight 2400 gm. Intraperitoneal injection of 80 mgm. of tuberculo-protein.

January 9, 1912. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Hα, containing 0.4 mgm. of bacilli. This suspension was about one-half the density of a twenty-four hour broth culture of typhoid bacilli.

On January 19 there was dyspnea, which lasted for three days, followed by apparent recovery. Six days later, there was evident wasting and the animal looked ill. On February 19 the rabbit was found dead in its cage.

Autopsy.—Emaciated, weight 1220 gm. No reaction at the site of inoculation. The lungs are voluminous and the pleura is studded with tiny gray and yellow nodules, up to 1.5 mm. in diameter. The lungs are congested and show patches of gelatinous consolidation and innumerable gray and yellow tubercles, 1 to 1.5 mm. in size. There is also a marked acute bronchitis.

The spleen is not enlarged and no tubercles are seen in it or in the liver. The peritoneum is smooth and glistening. The kidneys are congested and firm, and scattered through the cortex and pyramids are several miliary tubercles. The lymph glands are not enlarged or caseous.

Microscopic examination shows numerous acid-fast bacilli in the lungs. The tubercles in the lungs show numerous epithelial and giant cells and in most areas a central zone of coagulative necrosis. In the kidneys there are a few typical young tubercles.

January 11, 1912. Rabbit 6, white female, weight 2325 gm. Intraperitoneal injection of 75 mgm. of tuberculo-protein.

February 12. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Hα, containing 0.28 mgm. of bacilli and 2 ccm. of the same suspension subcutaneously in the left groin.

On the 16th of February, at the site of inoculation, there was a firm, yellow nodule, 1½ cm. in diameter, and two smaller nodes near the base of the ear. On February 20 these nodules had become larger and were white and fluctuating. On February 22 several new nodules, 4 cm. from the site of inoculation, appeared. (On this day the animal gave birth to a litter of four young.)

February 24. There was marked dyspnea and the animal was visibly emaciated. The dyspnea persisted until the 6th of March when there was practically air hunger, emaciation and cyanosis. The nodules in the ear had now almost disappeared. The pus made from one of the nodules shows numerous acid-fast bacilli.

March 20. Animal died at 10 a. m. Weight 1170 gm.

Autopsy.—The lungs are very voluminous, do not collapse and are practically non-air containing. Both are deep red in color, mottled with yellow and the parenchyma contains many tubercles, 1 to 2 mm. in diameter, some of which show advanced caseation.

There are a few tubercles seen in the slightly enlarged spleen. The liver is apparently uninvolved. The kidneys are pale and mottled with fairly numerous gray nodules; those in the cortex spreading as linear rays through the pyramids. The peritoneum shows a few gray tubercles and very numerous miliary tubercles on the posterior abdominal wall. The nodules in the ear, already described, show dense fibrous walls and central caseation.

Microscopic examination of the spleen, lungs and kidneys shows typical tubercles, some of which are undergoing caseation.

January 11. Rabbit 7, gray female, weight 2265 gm. Intraperitoneal injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Hα, which contained 0.28 mgm. of bacilli and simultaneously 2 ccm. of the same suspension into the tissues of the left groin. On February 16 there was a yellow nodule, 1 cm. in diameter, at the site of the intravenous injection. Four days later the nodule was enlarged and caseous and on the following day, two similar tumors appeared at the base of the ear. The animal was losing weight and on February 23 there was marked dyspnea, which became more intense and persisted until the 10th of March. It then became less marked, but there was a recurrence of dyspnea with tachypnea on March 24, which persisted until the death of the animal on the 4th of April.

Autopsy.—Weight 1290 gm. There are three caseating nodules in the left ear with yellow purulent contents, rich in acid-fast bacilli. The necrotic areas are well circumscribed and the cartilage beneath is eroded. The lungs are voluminous, reddish yellow in color and studded with tubercles 1 to 3 mm. in diameter. On section the parenchyma shows areas of broncho-pneumonia and numerous fresh and caseous tubercles, 0.5 to 2 mm. in diameter. There are no cavities seen. There is a marked secondary bronchitis and peribronchitis.

The liver is enlarged, but shows no definite involvement. The spleen is slightly swollen and soft. The peritoneum is clean. The kidneys are gray, swollen and firm with scattered tubercles in the cortex and medulla. In the left groin there is an enlarged and caseous lymph node.

Microscopic examination of the spleen, lungs and kidneys shows typical tubercles, with numerous giant cells and central caseation.

January 17, 1912. Rabbit 8, white male, weight 2260 gm. Intraperitoneal injection of 116 mgm. of tuberculo-protein. On February 12 the animal was given an intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Hα which contained 0.28 mgm. of bacilli and 2 ccm. of the same suspension into the subcutaneous tissues of the left groin.

Three days later a firm subcutaneous nodule appeared at the site of the intravenous inoculation, and on February 19 it was tense, yellow and measured 13 mm. in diameter.

February 25. Two new tumors have developed at the base of the ear, 3 cm. from the site of the inoculation. All the nodules are now softened and necrotic and the animal is slightly dys-

poneic. On March 5 the dyspnea was more intense, the rabbit was cyanotic and losing weight (2060 gm). On March 6 the dyspnea was less marked and the nodules in the ear had ulcerated through the skin. March 17 the animal died at 10.25 a. m.

Autopsy.—Weight 1630 gm. There are three nodules in the left ear, at or near the site of intravenous inoculation, which are caseous and on section show a fibrous wall and an eroded cartilagenous base. The contents of the tumors show numerous acid-fast bacilli. The lungs are collapsed and riddled with gray and yellow tubercles, 2 to 4 mm. in diameter. Small areas are atalectatic and hyperæmic, showing patches of broncho-pneumonia and marked bronchitis.

The heart is dilated, the myocardium is pale and flabby and there is a fresh warty vegetation on the anterior cusp of the mitral valve. The kidneys are pale and firm and a few yellow tubercles are seen in the cortex. Otherwise there is no evident tuberculosis.

Microscopic examination shows numerous tiny fresh tubercles with numerous giant cells, scattered through the lungs, and caseous tubercles in the cortex of the kidneys.

January 7. Rabbit 9, gray female, weight 1100 gm. Intraperitoneal injection of 85 mgm. of tuberculo-protein.

February 12. Intravenous injection of 2 ccm. of salt solution suspension of H_{α}, which contained 0.28 mgm. of bacilli and 2 ccm. of the same suspension subcutaneously into the left groin. On the 15th of February a firm, elevated nodule, 0.5 cm. in diameter, appeared at the site of the intravenous injection, and five days later this had increased to 1.4 cm. in size. On the 24th of February the surface of this tumor was ulcerated and covered with a brown crust. The animal was dull, looked ill and was losing weight (weight 980 gm.). On February 29 there was marked lethargy, anorexia and intense dyspnea. March 1, animal died at 3 p. m.

Autopsy.—The local lesions in the ear show central caseous plugs surrounded by an infiltrated zone and the ulceration has extended into the aural cartilage. A smear made from the contents of this ulcer shows numerous acid-fast bacilli. The lungs collapse normally, are deep pink in color and show no macroscopic tubercles. There are no manifest lesions of tuberculosis in the serous cavities, in the viscera or in the glands. Microscopic examination showed fairly numerous fresh miliary tubercles in the lungs.

January 31. Rabbit 10, white female, weight 1730 gm. Intraperitoneal injection of 22 mgm. of tuberculo-protein.

February 3 and 5. Intraperitoneal injection of 33 mgm. of tuberculo-protein.

February 27. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of H_{α}, which contained 0.3 mgm. of bacilli and a subcutaneous injection of 2 ccm. of the same suspension beneath the skin of the left groin.

From the time of inoculation until the 4th of March there were no symptoms and no reaction was visible at the sites of injection. On that day slight dyspnea developed and a tiny papule, ⅛ cm. in diameter, was noted at the site of the intravenous inoculation. Except for slight dyspnea and a progressive loss of weight (weight 1420 gm. on the 18th of March), the animal appeared in fairly good condition.

On March 20 this animal was etherized, together with control rabbit No. 14 which had received a larger dose of bacilli sixteen days before this rabbit was infected.

Autopsy.—Weight 1540 gm. No reaction found at the sites of inoculation. The lungs collapse partially on opening the chest, but show a surface greatly distorted by firm prominences and deep depressions. The eminences are made up of numerous tubercles, from 1 to 6 mm. in diameter, and the depressed areas consist of collapsed lung parenchyma. On section the lungs are riddled with yellow and gray tubercles, varying greatly in size. No extensive caseation, no large areas of consolidation and no cavities.

The liver is swollen but shows no macroscopic tuberculosis. The spleen is enlarged and soft with prominent Malpighian corpuscles and a few small yellow tubercles are seen. The kidneys are swollen, gray and the glomeruli stand out prominently. A few gray and yellow tubercles, 1 to 3 mm. in size, are seen through the capsule and, on section, these present as radiating rays through the kidney substance. The peritoneum is clean.

NOTE.—The picture here is in striking contrast to that seen in rabbit 14. The pulmonary involvment is incomparably greater, although both the infecting dose and the time elapsed since inoculation are less. The spleen, too, is more involved in this animal.

January 31. Rabbit 11, tan and white female, weight 1925 gm. Intraperitoneal injection of 22 mgm. of tuberculo-protein.

February 3. Intraperitoneal injection of 22 mgm. of tuberculo-protein.

February 5. Intraperitoneal injection of 33 mgm. of tuberculo-protein.

February 27. Intravenous injection into the lateral ear of 2 ccm. of a salt solution suspension of H_{α}, which contained 0.3 mgm. of bacilli and at the same time 2 ccm. of the same suspension beneath the skin of the left groin.

March 1. There is a small elevated nodule at the site of intravenous inoculation and two others proximal to it.

March 4. The animal is dyspneic and dull.

March 18. The dyspnea has ceased and the animal is in good condition. The nodule in the ear has increased in size, is soft and yellow.

September 19. Emaciated, lethargy and dyspnea have developed during the past week and the rabbit is rapidly losing ground.

October 1. The emaciation, torpor and dyspnea are extreme and there is a paralysis of the hind quarters.

October 5. Animal died.

Autopsy.—Emaciated rabbit, weight 1200 gm.

In the left ear, at the site of infection, there is a large, yellow caseous nodule, the contents of which are completely necrotic. The lungs are fairly voluminous, hyperæmic and much distorted by numerous yellow tubercles, many of which have coalesced to form caseous patches. The margins of the lungs are emphysematous. There are no cavities.

The kidneys are pale and swollen and in the cortex are several tubercles, pin head in size.

The other viscera show no macroscopic tuberculosis. (See *Note*, rabbit 15.)

Rabbit 12, gray male, weight 2075 gm. Received three sensitizing doses of tuberculo-protein, but died from an acute intercurrent infection before inoculation of tubercle baccili.

February 12. Rabbit 13, non-sensitized, white female, weight 1240 gm. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of H_{α}, which contained 0.28 mgm. of bacilli and 2 ccm. of the same suspension subcutaneously into the left groin.

Until the 28th of February the animal remained in good condition except for a small loss of weight. At this time the animal developed snuffles with frequent paroxysms of sneezing and a tenacious nasal discharge. The respiratory distress and emaciation were progressive and on March 1 the animal was found dead in cage.

Autopsy.—Weight 970 gm., great emaciation. No sign of reaction at the sites of inoculation. The lungs are voluminous, do not collapse, but are still air-containing, and float in water. The pleural surfaces are dull and dotted with numerous gray and yellow nodules, 0.5 to 0.25 cm. in diameter. On section the lung surface is red, mottled with yellow and here and there

are zones of consolidation about the bronchi with many gray and yellow tubercles throughout.

No tubercles are found in any of the other viscera. Microscopic examination of sections of the lungs shows typical young and caseating tubercles and areas of polymorphonuclear infiltration. The giant cells here, however, are fewer in number than those seen in the sections of the sensitized animal.

February 12. Rabbit 14, white female, weight 1200 gm., non-sensitized control. Intravenous inoculation into the lateral ear vein of 2 ccm. of a salt solution suspension of Ha, containing 0.30 mgm. of bacilli and 2 ccm. of the same suspension subcutaneously into the left groin.

On February 22 three yellow nodules, 0.5 cm. in diameter, were visible at or near the site of the intravenous injection. These increased in size and a week later, the largest had ulcerated through the skin. At no time until May 20, when the animal was etherized, did any signs of respiratory distress develop, the only sign apparent being slight emaciation. On May 20 the animal was etherized in order to compare the lesions here present with those that had developed in sensitized rabbit 10.

Autopsy.—Weight 1380 gm. (pregnant). The lungs are hyperæmic and slightly edematous. At and near the upper pole of both upper lobes are several nodes, 1 to 4 mm. in diameter, which project above the general surface of the organs, are yellow in color and very firm on palpation. The rest of the parenchyma is air-containing and only a few small tubercles are seen.

There are no tubercles seen in any of the other organs. The uterus contains six embryos, about ten days of age.

Microscopic examination shows caseating tubercles in the upper lobes of the lungs, few in number and showing fewer giant cells than were seen in the tubercles in rabbit 10.

February 27. Rabbit 15, non-sensitized, white male, weight 1900 gm. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Ha, which contained 0.3 mgm. of bacilli and at the same time 2 ccm. of the same suspension into the subcutaneous tissues of the left groin.

In the course of three weeks a small nodule appeared at the site of the intravenous inoculation, which soon ulcerated and finally healed. The animal remained in good condition until the week of September 1, when emaciation rapidly developed and the animal became dyspneic and dull. It died on October 15.

Autopsy.—Emaciated rabbit, weight 1200 gm. There is no reaction at the sites of inoculation.

The lungs are voluminous, do not collapse when the chest is opened, are everywhere adherent to the thoracic wall, and the dense fibrous pleural adhesions are broken with difficulty. The lungs themselves are hyperæmic and completely riddled with caseous areas, leaving little lung tissue to be seen. A large cavity almost replaces the left lower lobe, another, slightly smaller, is found in the right lower lobe and several smaller vomicæ occur throughout the organs.

Except for the kidneys the other viscera show no tuberculosis and in the kidneys only a few small cortical lesions are found.

NOTE.—This is the most striking instance of cavity formation noted in any of our experimental animals. The pulmonary involvement is far greater than in the sensitized rabbit 11 and it is interesting that although the latter lived almost as long, no vomicæ were found in the lungs.

February 27. Rabbit 16, non-sensitized, white male, weight 2250 gm. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Ha, which contained 0.28 mgm. of bacilli and at the same time 2 ccm. of the same suspension beneath the skin of the left groin.

Until June 7 the animal looked well and was gaining weight, but it then became dull, fed poorly and showed beginning emaciation and on June 12 it was etherized.

Autopsy.—There is no local reaction at the site of the inoculations. The lungs are hyperæmic and thickly studded with gray and yellow tubercles, 1.5 to 3 mm. in size, but in large part are air-containing and still float in water. The pleural surfaces show many tubercles, although not so numerous as in the sensitized mate. There is parenchymatous degeneration of the other viscera, but no further macroscopic evidence of tuberculosis.

Microscopic examination shows typical tubercles throughout the lungs.

March 7. Rabbit 17, white female, weight 1930 gm. Intraperitoneal injection of 90 mgm. of tuberculo-protein.

March 30. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

May 1. The animal is now emaciating and is slightly dyspneic. There is no reaction at the site of infection.

May 11. The dyspnea has ceased and the rabbit is in fairly good condition.

July 2. Etherized and sectioned for a comparison of the extent of the disease with that produced in the control rabbit 22.

Autopsy.—Under nourished rabbit, weight 1700 gm. There is no local reaction at the point of inoculation.

The lungs are voluminous with irregular surfaces distorted by elevations and depressions. Scattered through the parenchyma are many fresh gray tubercles and very numerous caseating yellow nodules from 1.5 to 5.5 mm. in diameter.

The kidneys are pale and there are fairly numerous small yellow cortical tubercles in both organs. The other viscera show no tuberculous involvement.

March 7. Rabbit 18, white female, weight 1720 gm. Intraperitoneal injection of 85 mgm. of tuberculo-protein.

March 30. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

April 27. There is slight dyspnea and a slight loss of weight (1670 gm.).

June 2. Etherized.

Autopsy.—Emaciated rabbit, weight 1480 gm. There are numerous subpleural tubercles and throughout the parenchyma of both lungs there are innumerable yellow caseous nodules, some of which have coalesced to form necrotic placques. A few of these show well-defined encapsulation. The spleen and the kidneys are swollen and both contain fairly numerous tiny tubercles. The other viscera show no tuberculous involvement.

March 7, 1912. Rabbit 19, white female, weight 1900 gm. Intraperitoneal injection of 95 mgm. of tuberculo-protein.

March 30. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

April 1. There is no reaction at the site of inoculation, and no symptoms have developed.

May 4. Etherized and lesions compared with those found in rabbit 20, its control mate.

Autopsy.—Weight 1750 gm. There are no lesions in the ear. The lungs are partially collapsed and dotted here and there with large tubercles up to 0.5 cm. in diameter, several of which are caseous. The interstitial tissue is congested and edematous.

The liver is large and soft and shows no evident tuberculosis. The spleen is enlarged and shows a few gray tubercles. The kidneys show cloudy swelling, and numerous subcapsular gray tubercles. The retroperitoneal fat is very small in amount.

Microscopic examination of the spleen, the lungs and the kidneys shows typical tuberculosis.

March 30. Rabbit 20, white female, weight 1940 gm., non-sensitized control. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

April 28. There is no evidence of a local reaction at the site of inoculation and no respiratory distress, but there is rapid emaciation and lethargy.

May 3. The emaciation is progressive, the animal is dull, has diarrhea, and looks more like an animal with coccidiosis than like those we have seen die of tuberculosis.

May 4. Dead in cage.

Autopsy.—Weight 1370 gm., emaciated. Lungs red and collapsed, studded with firm, gray tubercles up to 0.4 mm. in diameter, some umbilicated and fibrous. The peritoneal cavity contains numerous cysts, up to 1.25 cm. in size. The omentum is distorted by many cysts and a thick exudate, and the liver is mottled with fresh lesions of coccidiosis. There is no macroscopic tuberculosis of the liver, spleen, kidneys or lymph nodes.

Microscopic examination shows young and older tubercles in the lungs, the latter with beginning fibrosis at their periphery.

March 30. Rabbit 22, white female, weight 2030 gm., non-sensitized control. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Hα, which contained 0.07 mgm. of bacilli.

July 2. Since inoculation there has been no evidence of a local reaction and no symptoms have developed. Etherized.

Autopsy.—Well nourished rabbit, weight 1810 gm. There is no reaction at the site of infection. The lungs show numerous caseous nodules from 2 to 14 mm. in diameter, a few of which are encapsulated. There are no fresh tubercles and there is no cavity formation. No tubercles are seen in any of the other viscera except in the kidneys, in which a few yellow cortical tubercles are found.

Note.—The pulmonary lesions in this animal are more advanced than in the sensitized mate, but the renal involvement is less marked.

March 20. Rabbit 23, white female, weight 1590 gm. Intraperitoneal injection of 80 mgm. of tuberculo-protein.

April 10. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Hα, which contained 0.07 mgm. of bacilli. No reaction at the site of the intravenous inoculation, no symptoms other than progressive emaciation had developed from the time of inoculation until the animal was etherized, together with control rabbit 27, on May 18.

Autopsy.—Weight 1120 gm. The lungs are deep pink in color and show a surface much distorted with tubercles of all sizes, from a pin point to a pin head in diameter; some are fresh and gray, others yellow and caseating; none are fibrous. Everywhere the parenchyma is studded with tubercles between which the tissue shows congestion and edema.

The liver is swollen but shows no evident tuberculosis and only a few old lesions of coccidiosis. The spleen is enlarged, firm and contains many tubercles. The kidneys are congested and show numerous tiny gray and yellow subcapsular tubercles, which on section appear as linear rays through the cortex and the pyramids. The mesenteric lymph glands are slightly enlarged.

Microscopic examination of the lungs and of the kidneys shows typical tubercles with many giant cells.

NOTE.—The pulmonary involvement is greater than that shown by control rabbit 27, although both received the same infecting dose, were allowed to live the same number of days and were housed together in the same cage. The renal and the splenic lesions, too, are more extensive here than in the control.

March 20. Rabbit 24, white female, weight 1800 gm. Intraperitoneal injection of 80 mgm. of tuberculo-protein.

April 10. Intravenous injection into the lateral ear vein of 1 ccm. of a saline suspension of Hα, which contained 0.14 mgm. of bacilli.

June 18. No symptoms have developed and no local reaction has appeared at the site of inoculation since the animal was infected. Etherized.

Autopsy.—Well nourished female (pregnant) rabbit, with good panniculus. The lungs are fairly voluminous and for the most part air-containing, although riddled with firm tubercles, 1 to 2 mm. in size. The pleural surfaces are irregular, pink in color and mottled with yellow nodules. On section innumerable tubercles, 1 to 3 mm. in size, are seen in the collapsed parenchyma, a few of which are undergoing caseation. The liver is swollen, as is also the spleen, but in neither are tubercles visible. The kidneys show a striking picture. They are pale red in color, swollen and beneath the capsule many gray and yellow tubercles, 0.5 and 1.0 mm. in diameter are seen. On section the markings are clearly defined, and the cortical tubercles stand out sharply. The pelvis of the right kidney is greatly dilated. There is no glandular involvement.

Microscopic examination shows typical tuberculosis of the spleen, the lungs and the kidneys.

March 20. Rabbit 25, Maltese, with white face, female, weight 2050 gm. Intraperitoneal injection of 90 mgm. of tuberculo-protein.

April 10. Intravenous injection into the lateral ear vein of 1 ccm. of a salt solution suspension of Hα, which contained 0.14 mgm. of bacilli.

No symptoms developed in the animal and it was etherized on June 7 for a comparison of the lesions with those developed in control rabbit 28.

Autopsy.—Weight 1820 gm. The lungs show scarcely any normal parenchyma, the organs being completely riddled with tubercles, 0.5 to 1.5 mm. in diameter.

The spleen and the liver show no macroscopic tuberculosis. The kidneys are swollen and congested and a few subcapsular gray tubercles, pin head in size, are seen.

April 10. Rabbit 28, Maltese, with white paws, female, weight 1878 gm., non-sensitized control. Intravenous injection into the lateral ear vein of 1 ccm. of a salt solution suspension of Hα, which contained 0.14 mgm. of bacilli. From the time of inoculation until June 6 when the animal was found dead in its cage, no symptoms other than emaciation were noted.

Autopsy.—Weight 1570 gm. The lungs are collapsed and studded with many large yellow caseous tubercles, firmly walled off by dense fibrous tissue. The interstitial tissue is hyperæmic, but shows relatively few tubercles, as compared with the lungs of rabbit 25.

The liver is swollen and shows numerous fresh lesions of coccidiosis. The spleen is small and quite normal in appearance. The kidneys are swollen and congested, but show no macroscopic tubercles. The peritoneal cavity contains many parasitic cysts.

NOTE.—The lesions are slightly more extensive in rabbit 28 than in the control animal, although the difference is not so striking as that seen in other pairs. Perhaps the intercurrent coccidiosis in the control is responsible, to some extent, for the greater advance of the tuberculous process in it. The walling off and caseation of the lesions in the lungs of the control animal suggest a greater resistance to infection than does the miliary involvement in the sensitized rabbit.

April 10. Rabbit 26, white male, weight 2050 gm., control, non-sensitized animal. Intravenous injection into the lateral ear vein of 1 ccm. of a salt solution suspension of Hα, which contained 0.14 mgm. of bacilli.

June 18. The animal is in good condition, and has shown no symptoms since the time of inoculation. Etherized, together with sensitized rabbit 24, for a comparison of the lesions.

Autopsy.—Weight 2005 gm. The lungs are voluminous and show a greater involvement, with a further advance of the lesions, than do the lungs of the sensitized mate. Although in great part air-containing, the parenchyma shows areas of gelatinous translucent consolidation with numerous tubercles, gray or yellow in color. These vary in size from 0.5 to 1.7 mm. and several of

the largest are completely necrotic. Some have a definite fibrous investment.

The liver, the spleen and the kidneys show no evidence of tuberculosis.

April 10. Rabbit 27, white female, weight 1850 gm., control, non-sensitized animal. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

May 18. Etherized with its sensitized mate, rabbit 23.

Autopsy.—Weight 1400 gm. There is no reaction at the site of the intravenous inoculation. The lungs are pink in color, the pleural surfaces distorted by fairly numerous tubercles up to 2 mm. in size. Between these the parenchyma is hyperæmic, but unlike the lungs of rabbit 23 does not show as much infiltration with tubercles. The contrast is striking for there is an incomparably greater advance of the infection in the sensitized animal than is seen here.

The liver is enlarged and congested but no tubercles are seen. The spleen is not enlarged and a few tiny tubercles are seen through the pulp. The kidneys show a few tubercles, pin point in size and gray in color. At the lower pole of the left kidney there is a large yellow patch of firm, yellow necrosis and there are some fresh lesions of coccidiosis in the mesentery.

Microscopic examination shows typical tubercles in the lungs, spleen and kidneys.

TABLE VI

Rabbit		Preliminary treatment	Infecting dose of tubercle bacilli	Duration of life after infection	Tuberculosis					Remarks
Number	Mate				Lungs	Liver	Spleen	Kidneys	Local	
		Tuberculo-protein	*mgm.*	*Days*						
5	..	80 mgm.	0.4	* 41	+++	—	—	+	—	Dyspnea after 10 days
6	..	75 mgm.	0.56	* 36	+++	—	+	++	+	Dyspnea after 12 days. Litter
7	16	do.	0.56	* 51	+++	—	+	++	+	Dyspnea after 11 days
8	..	116 mgm.	0.56	* 33	+++	—	—	+	+	Dyspnea after 13 days
9	13	85 mgm.	0.56	* 17	+	—	—	—	+	Dyspnea after 17 days
10	14	88 mgm.	0.60	† 82	+++	—	+	+	+	Slight dyspnea after 5 days
11	15	77 mgm.	0.60	*220	+++	—	+	++	++	Dyspnea after 8 days
13	9	None	0.56	* 18	+++	—	—	—	—	Snuffles (rabbit septicæmia)
14	10	do.	0.60	† 97	+	—	—	—	+	No dyspnea. Pregnant
15	11	do.	0.60	*230	++++	—	++	++	+	Marked vomica formation
16	7	do.	0.56	†105	++	—	—	—	—	No dyspnea
17	22	90 mgm.	0.07	† 94	+++	—	++	++	—	Slight dyspnea after 31 days
18	..	85 mgm.	0.07	† 94	+++	—	++	++	—	Dyspnea after 28 days
19	20	95 mgm.	0.07	† 35	++	—	++	++	—	No dyspnea
20	19	None	0.07	* 35	++	—	—	—	—	Coccidiosis
22	17	do.	0.07	† 94	+++	—	+	+	—	No dyspnea
23	27	80 mgm.	0.07	† 38	+++	—	++	++	—	No dyspnea
24	26	do.	0.14	† 69	+++	—	+++	+++	—	No dyspnea
25	28	90 mgm.	0.14	† 58	+++	—	+	+	—	No dyspnea
28	25	None	0.14	* 57	++	—	—	—	—	Coccidiosis
26	24	do.	0.14	† 69	+++	—	—	—	—	No dyspnea
27	23	do.	0.07	† 38	+	—	+	+	—	No dyspnea

* Died. † Etherized.

The findings in this series of experiments are unique, for so far as we have been able to determine, an acute lethal tuberculosis had not previously been produced in rabbits with the small infecting doses of human type tubercle bacilli here used. Several of the sensitized rabbits after inoculation developed the clinical picture described by Theobald Smith in rabbits inoculated with the bovine type of the organism. Eight of the sensitized animals developed dyspnea, and five died from tuberculosis within sixty-seven days after inoculation. In five sensitized and in two control animals, tubercles developed at or near the site of the intravenous inoculation. The significance of this is not clear, inasmuch as, contrary to expectation, the animals in which it developed showed no apparent difference in general reaction from that shown by those in which no local lesion developed. With the exception of two pairs of animals, the tuberculosis which developed was more extensive and more severe in the sensitized rabbits than in the non-sensitized infected controls. Certainly it is evident that in most of the rabbits resistance to moderate sized doses of human type tubercle bacilli—doses smaller than those used by Theobald Smith in his classical experiments—is lowered by sensitizing with our protein. What the effect of hypersensitiveness on infection with very minute doses would be, we have no evidence to show.

The results of the above cited experiments are interesting. They offer material for thought and for the formation of hypotheses. For the present, however, it seems wiser not to theorize but to rest content with a statement of the facts.

In no instance can the diminution of resistance to infection when it occurred be attributed to the treatment of the animals with too large amounts of the protein used, for amounts were never administered in great excess of that required actively to sensitize. Similarly the doses of tubercle bacilli used to infect were quantitatively estimated, were no larger than those ordinarily employed in similar work and the bacilli inoculated were of low virulence. The results of the experiments on rabbits are especially striking, but it is to be definitely asserted that though it was the rule to find more intensive infection in the sensitized animals than in the non-sensitized controls, still the production of a rapidly fatal tuberculosis in rabbits by inoculation of human type bacilli was inconstant, indeed exceptional.

The experiments already detailed show definitely that in animals with preexisting hypersensitiveness to the tuberculoprotein which we have used, there is in the majority a diminished resistance to infection with tubercle bacilli of the human type and that in a large number of cases no alteration of resistance is to be noted. From these facts it seems clear that hypersensitiveness to this protein was not protective against the small amounts of tubercle bacilli injected, but that it was a neutral or even a baneful factor in the immunization of the animals. It would be interesting to see if sensitization with a tuberculoprotein would afford protection against a subsequent infection with single bacilli or with a very few organisms. The observations we have made upon this phase of the problem have led to no conclusions.

From the data to be gathered from the literature and from an analysis of our observations, broad conclusions do not seem justifiable, nor should any positive correlative inferences with the effects of tuberculin be drawn.

Too few accurate investigations on the constitution of the bacillus tuberculosis have been made to warrant the statement that hypersensitiveness to a particular protein extracted from the bacilli will exercise the same influence on subsequent infection as that which a protein prepared from the organisms

by another method might produce. It does not seem entirely improbable that the protein composition of the bacterium in question may be a complex rather than a simple one; that the protein content of the organisms may be a composite content, consisting of more than a single type of protein substance. A small amount of evidence for such a tentative view is furnished by the variability in the sensitizing power of protein obtained by the method we have used when the time of extraction or the temperature at which the extraction proceeds is altered. Again a dose of one commercial tuberculin at times fails to produce any reaction in a tuberculous host, when an equal dose of what purports to be an identical preparation elicits a well-marked response and vica versa.

Further, with reference to the action of tuberculin in man, it seems unwise to draw inferences from these experiments until the identity of the tuberculo-protein in tuberculin and that obtained by aqueous extraction of tubercle bacilli shall have been established. Work upon this problem is now being carried on in this laboratory.

For the present the following conclusion seems justified:

Hypersensitiveness produced in guinea-pigs and in rabbits by sensitization with a protein obtained from the bacillus tuberculosis, human type, by water extraction, exerts a baneful or a neutral influence on a subsequent tuberculous infection. Whether or not a similarly produced condition of hypersensitiveness would influence differently the course of infection with a very few organisms cannot be stated.

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A CONSIDERATION OF THE MILK SUPPLY OF BALTIMORE.

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In common with other large cities, Baltimore is faced with the important and complicated problem of its milk supply. The rôle which this product plays in nutrition, having served from time immemorial as one of the chief foods of the human race, is unfortunately not the only relation which it occupies towards man. It is also one of the chief agencies in the transmission and spread of disease. Milk may convey to man, for instance, certain infections of the animals producing it such as Malta fever, tuberculosis, foot and mouth disease, and may spread from individual to individual such diseases of man as typhoid fever, diphtheria and tuberculosis. In addition the summer diarrhœas of children are somehow or other related to an impure milk supply which must assume the responsibility also for such maladies as "septic sore throat" although here it is by no means clear whether the organisms causing the infection are derived from man or animals. As a result of this peculiar relation to us the question of milk becomes at once extremely important. City officials must not only see that this food when delivered to the consumer has a definite nutritive value, they must guarantee, if possible, that it will not produce illness among those who use it, to which end they must insist upon the most rigid regulations to prevent its contamination by bacteria pathogenic for man. It is by no means easy, however, to determine how this can be accomplished and during the past few years we have seen in America most elaborate chemical and bacteriological studies of milk and exhaustive investigations of the conditions under which it is produced. In such cities as Washington, New York, Boston, Philadelphia and Rochester municipal employees, laboratory investigators and private philanthropists have united in the effort to discover the measures which must be adopted in order that milk of a satisfactory character may be obtained. It is agreed that milk from unhealthy animals, from animals suffering from tuberculosis, particularly tuberculosis of the udder or from inflammatory conditions of the udder must be excluded from sale. Furthermore, milk produced under unhygienic conditions, improperly handled at the dairy farm, during transportation, or by the retailer must also be excluded, not because such milk is in itself an improper food, but because it is more likely to be contaminated by disease-bearing germs. As the most convenient and satisfactory method of determining whether the various avenues are closed by which milk may be polluted, bacteriologists now almost universally depend upon a bacterial count, that is an estimation of the number of ærobic organisms in the milk. Various cities have adopted different standards forbidding the sale of milk containing more than a certain number of organisms. These standards vary from thirty thousand to one million bacteria per cubic centimeter as the highest number of organisms which milk may contain and still be lawfully sold. It must be remembered, however, that the ærobic bacteria which are counted in milk are species which may be regarded as perfectly normal to it, and that they are, at least in most instances, without pathogenic properties. Indeed from the theoretical standpoint it is difficult to understand why milk containing a large number of the organisms indigenous to it is of a different nutritive value or is more likely to convey disease than milk with a small number of germs of the same character. Nevertheless, there is a good deal of clinical evidence for the view that excessive numbers of bacteria in milk may be productive of intestinal disturbances. Aside from theoretic laboratory questions or clinical discussions the estimation of the number of bacteria gives us the best possible information as to the conditions under which the milk is originally obtained at the

dairy farms, and during its transportation, the temperature at which it is kept, and its age. From practical experience in large cities, it may now be regarded as essential in maintaining the health of communities that milk containing an excessive number of bacteria must be excluded from sale or sold under rigid precautions, not merely because of the danger which these bacteria themselves present to man but because they are so likely to be accompanied by the germs of specific disease.

The milk in Baltimore varies greatly in character. On the one hand we have a number of dairies which sell bottled milk of a high degree of purity, the owners and managers of these dairies endeavoring conscientiously to live up to the dictates of modern knowledge in regard to the handling of this product. On the other hand we have large quantities dispensed in small shops and corner groceries under the filthiest conditions, and coming from dairies where no proper measures of cleanliness are carried out. We have thus a marked difference in the quality of the milk used by the rich or well-to-do and by the poorer classes. The complexity of the situation is indicated by the fact that there are over 4000 stores in Baltimore which dispense milk, the majority of these stores supplying it over the counter, the so-called "dipped milk." The amount of bottled milk sold here is increasing, however, and of this amount a considerable proportion is pasteurised, that is, heated to a temperature sufficient to destroy not all but a large number of the organisms present in it. The Baltimore milk supply comes from nearly 2400 farms in Maryland and the milk question is, therefore, a state as well as a city one.

The Department of Health of Baltimore has been grappling with the problem for some years and in their various publications may be found interesting and valuable data in regard to the milk sold here. For some time we have been interested in the question from the laboratory standpoint and on various occasions have made systematic examinations of the milk purchased from the small shops in the vicinity of The Johns Hopkins Hospital. Our results are much the same as those of the city Department of Health. The milk problem must be attacked from various standpoints, however, and by a number of different investigators if good is to be accomplished. I wish to call attention, therefore, to the data obtained in the year 1911 by Dr. de Angulo and in 1912 by Mr. Joseph.

REPORT FOR 1911.

By Cary Fink de Angulo, M. D.

During the five months of 1911 from January to June we examined a large number of samples of milk collected in various small shops in Baltimore. The conditions under which this milk was distributed were so unsatisfactory, there was so great an opportunity manifest for contamination by bacteria that it seemed quite impossible to classify the distributing centers in any satisfactory way. Our samples were obtained in part from East Baltimore, but many were collected in the western and southern sections of the city in the poorer districts. They represent the "dipped milk" sold so commonly to the poor people of this city. At no shop visited could the conditions be described as satisfactory. The supply of ice was usually quite insufficient, much of the milk was kept in open vessels and slovenly attendants were employed to handle it, usually with dirty utensils. Various methods of making bacterial counts were employed at different times but eventually we came to regard gelatin plates kept at room temperature, 48 to 72 hours, as the most reliable. Endo's medium was used on a group of samples with a view to discovering the number of *Bacillus coli* forms present, but the results were in general not so satisfactory as those obtained from a dextrose fermentation tube. The data found in this way proved interesting but the results were not sufficiently constant to indicate a definite relation between the bacterial count and the extent of fermentation. At the same time the Smith tube gives us valuable information about milk and further work may reveal some law by which the extent of fermentation may be used as an index of pollution as in the study of water. From among the many examinations made we have selected 25 which illustrate our results in a general way. The average of the 25 samples was a trifle less than nine million bacteria per cubic centimeter which may be regarded as fairly high considering the fact that the samples were collected in cold or moderate weather. With the exception of No. 3, the first nine samples examined during the winter showed but a relatively small number of bacteria, whereas the samples collected later in the year showed usually a much higher count.

MILK EXAMINATIONS IN 1911.

Sample No.	Date	Bacterial Count	Fermentation of Dextrose in Dilution
1	1/21	500,000	1-1000 negative
2	1/30	2,600,000	1-1000 positive
3	2/7	10,000,000	1-10,000 positive
4	2/11	1,300,000	1-1000 negative
5	2/4	3,000,000	1-100 positive
6	2/17	1,300,000	1-10,000 positive
7	3/14	1,800,000	
8	3/16	1,200,000	
9	3/20	1,225,000	
10	3/27	6,200,000	
11	3/28	46,000,000	1-1000 negative
12	3/30	5,200,000	1-1000 positive
13	3/31	35,700,000	1-1000 positive
14	4/4	5,000,000	1-1000 positive
15	4/21	6,780,000	1-1000 positive
16	4/24	11,700,000	
17	4/25	6,200,000	1-1000 positive
18	4/28	5,500,000	1-100 negative
19	4/28	21,000,000	1-100 negative
20	5/5	13,000,000	
21	5/8	4,560,000	1-100 negative
22	5/8	1,400,000	1-100 positive
23	5/15	21,400,000	1-1000 positive
24	5/15	8,900,000	1-1000 positive
25	5/16	12,000,000	1-1000 positive

REPORT FOR 1912.

By Morris Joseph.

In the spring months of 1912 we were enabled to make a systematic examination of the market milk sold in East Baltimore. The various shops and corner grocers from which milk is distributed were visited personally, careful notes made of the conditions found, a sample of milk obtained and taken to

the laboratory for examination. As a result of the procedure adopted in collecting the specimens it was possible to study but a limited number. The method of examination employed was that which obtains usually in such work. Various dilutions of the milk were made and planted in agar and in fermentation tubes. The plates and tubes were then incubated at 37° C. Agar plates and the body temperature were selected for the work in order to determine whether any correlation exists between the bacterial count and the fermentation reactions, although it is well known that gelatin at room temperature gives higher bacterial counts for milk than agar at 37° C. The various data obtained in this investigation have been arranged in the accompanying chart. A number of interesting points may be mentioned in regard to it. The lowest count, fourteen thousand, was given by a sample of pasteurised milk obtained from a delivery wagon while the highest count, thirty million, was obtained from a dirty shop with poor ice supply, a shop under suspicion and supervision of the Board of Health. There is in general a correlation between the bacterial count and the general conditions of handling the milk. This correlation is by no means exact, however. One can only say that where excessive numbers of bacteria were found in the milk a reason could be seen in the method of handling as in sample No. 7 where over thirteen million bacteria were found on examination and the milk had been kept in an uncovered pitcher, or in sample No. 15 where a count of over seventeen million was obtained from milk sent to Baltimore from Pennsylvania and necessarily long in transit. All the samples of dipped milk which showed a low bacterial count, that is, under one million, as in samples Nos. 1, 2, 6, 12, 16, 18 were from shops where the general conditions, especially as to the ice supply, were excellent, while other specimens in which the bacteria were few in number were either fresh milk as in sample No. 5 or bottled milk as in sample No. 13. Two of the wagon samples, Nos. 11 and 14, showed a low bacterial count while the third sample from a wagon, No. 23, which showed a count of over a million had been insufficiently protected by ice. In 5 cases, samples Nos. 8, 9a, 17, 21 and 24, a high bacterial count is distinctly associated with poor ice supply or careless methods of handling. In other instances such a count is not explained by any conditions observed in handling as in sample No. 25 where over ten million bacteria were found in a cubic centimeter of milk from an excellent shop. It is evident that the conditions under which milk is handled, its protection by ice, its age, all are of definite influence in determining the bacterial content, but that the question is extremely complicated owing to a number of other factors such as the conditions at the dairy farm, the period of time during which the milk is in transit and its refrigeration at this time.

In general there is no definite relation between the bacterial counts and the extent of fermentation. This is not surprising in view of the fact that our counts are made of all varieties of bacteria both fermenters and non-fermenters. The observations on this point, however, are too few in number to give us any exact information.

MILK EXAMINATIONS IN 1912.

Sample No.	Date	Bacterial count	Fermentation in dextrose positive in dilution of	Remarks
1	4/12	226,000	1-1000	Shop clean. Milk carefully handled. Sufficient ice supply.
2	4/12	817,750	1-1000	Shop clean. Milk and utensils carefully handled. Insufficient ice supply.
3	4/15	14,000	1-10	Pasteurised milk from wagon. Wagon clean. Driver neat and careful.
4	4/15	30,222,000	1-100	Shop clean but attendants dirty. Ice supply insufficient on first visit but satisfactory on second visit.
4a	4/22	3,070,000	1-100	This shop was under Board of Health supervision.
		Samples Nos. 4 and 4a were from same dairy.		
5	4/19	250,000	1-1000	Shop crowded. Woman in attendance careless and untidy. Ice supply limited. Sample was from fresh milk.
6	4/22	510,500	1-10,000	Shop fairly clean. Milk properly handled. Insufficient ice.
7	4/26	13,768,750	1-10,000	Shop clean. Owner neat. Milk kept in earthen pitcher uncovered. No ice supply.
8	4/26	4,137,750	1-10,000	Shop was in a filthy condition, stuffy and crowded. Owner and wife careless and slovenly. Utensils dirty. Ice insufficient.
9	4/29	1,244,500	1-10,000	Shop small, fairly clean. Milk cans open.
9a	5/3	11,875,000	1-10,000	No ice supply. Girl in attendance clean and careful.
		Samples Nos. 9 and 9a were from same shop.		
10	4/29	5,952,250	1-10,000	Shop and attendant very clean. Milk carefully handled.
11	5/6	423,600	1-1000	Wagon sample. Driver and utensils clean. Milk carefully handled.
12	5/6	510,600	1-100,000	Shop and utensils clean. Milk cold and carefully handled.
13	5/10	562,000	1-10,000	Sample of bottled milk from supply used in manufacture of ice cream. Shop clean. Owner careful.
14	5/10	106,250	1-1000 neg.	Sample from wagon. Driver careless. Ice sufficient.
15	5/13	17,720,000	1-1000	Sample of milk sent from Pennsylvania on railroad. Shop and owner clean and neat.
16	5/13	697,500	1-1000 neg.	Shop untidy. Attendant clean. Ice sufficient.
17	5/17	8,700,000	1-1,000,000	Shop and woman in attendance clean. Sufficient ice. Milk carelessly handled.
18	5/17	704,000	1-1000	Shop and attendant clean and neat. Ice supply sufficient.
19	5/20	2,460,000	1-100,000	Shop and attendants neat, clean, and milk carefully handled. Ice protection sufficient.

Sample No.	Date	Bacterial count	Fermentation in dextrose positive in dilution of	Remarks
20	5/20	1,381,500	1-1000	Store and woman in charge clean. Milk carefully handled. Utensils clean. Ice sufficient.
21	5/24	21,094,000	1-10,000	Shop and attendants untidy and dirty. Milk carelessly handled. Insufficient ice supply. This shop caters chiefly to negroes.
22	5/24	11 227,000	1-1000	Shop and woman in charge clean. Milk carefully handled. Sample represented a remnant of milk left in the can.
23	5/27	1,243,000	1-1000	Wagon sample. Wagon and driver clean. Insufficient ice.
24	5/27	1,620,000	1-10,000	Store and boys in charge clean. Milk protected by ice, but carelessly handled.
25	5/27	10,210,000	1-100,000	Shop clean. Man in charge neat in appearance. Milk carefully handled and protected by ice.

MALUM PERFORANS IN DIABETES MELLITUS.

A REPORT OF SEVEN CASES.

By JOHN T. SAMPLE, M. D., and W. L. GORHAM, M. D.

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Malum perforans or *mal perforant* in diabetes mellitus was first described by Marquez[1] in 1866, although it was Puel[2] who, some nine years later, called attention to its not infrequent occurrence in that disease. Since 1875, there have been numerous communications on the subject by various observers [Clement (1881); Kirmisson (1885); Jeannel (1886); Heusner (1885); Laffon (1885-6); Wessinger (1889)]. Naunyn[3] in 1895 reported seven cases in his large series of diabetic cases and Adrian[4] sometime later collected an extensive bibliography.

At the request of Professor Barker we have made a study of the clinical aspects of *mal perforant* as a complication of diabetes mellitus based upon the findings in seven cases admitted to The Johns Hopkins Hospital.

The first and sixth cases of this series were studied by us personally, the details of the others were taken from the hospital records.

CASE 1 (Medical No. 26835).—G. K., æt. 51, white, single, a solicitor, was admitted to the hospital January 18, 1911.

Complaint: "Sores on the feet."

Family History: One sister died of diabetes; otherwise negative and unimportant.

Past History: General health has always been good. He is constipated, as a rule, eats heartily but not of sweets especially. Does not use alcohol or tobacco. Walks a great deal on city pavements.

A little over 10 years ago patient was operated upon in The Johns Hopkins Hospital for a large carbuncle on back of neck. Sugar (2 per cent) was found in the urine at that time, but there were no other symptoms of diabetes. He felt perfectly well and after five days on a restricted diet became sugar-free, and was discharged. Patient admits instructions given about diet were not followed.

He returns to the hospital with ulcers on both feet of seven weeks' duration. The first one appeared on the dorsum of the fifth toe, followed by a larger one on the dorsum of the left foot, and later by one on the external malleolus. They grew progressively worse and pus was discharged. Soon after this an ulcer appeared on the plantar surface of the right foot. About five weeks before admission he was compelled to stop work, because he could not walk. Patient has had no other symptoms. No bulimia, polydipsia, polyuria, nycturia, pruritus, cataract, skin infections or loss of weight.

Physical Examination: Patient is of moderate frame, rather obese; skin pasty, conjunctivæ pale, hearing impaired. Teeth in bad condition, many absent, gums slightly retracted. Scar of old carbuncle on neck. There is slight general glandular enlargement. Thorax is barrel-shaped. Heart and lungs are normal. Pulse slow, regular, low tension, radials moderately thickened. Abdomen negative. There is no trophic disturbance of fingers. Deep reflexes of arms are present. No œdema of ankles. Considerable pigmentation and many irregular scars on shins. The reflexes are present and normal.

Right Foot: Fairly good pulse in the dorsalis pedis and posterior tibial arteries although both vessels are sclerotic. Over the metatarsal phalangeal joint of first toe is a scabbed area surrounded by desquamation and on plantar surface just back of balls of toes there is a large bluish desquamating area.

Left Foot: Good palpable pulse in both dorsalis pedis and posterior tibial artery. On the dorsum of foot on either side of ankle are small reddish areas capped with scabs surrounded by desquamation. On the dorsum of the big toe is a discharging sinus filled with creamy pus. At the base of the sinus, made up of coarse granulations, a probe can be passed a quarter of an inch forward toward the nail and fully an inch backward toward the ankle. Both sinuses are superficial and do not come in contact with bone. The fifth toe is swollen and shows a similar sinus on its dorsum, discharging pus. Sense of touch is well preserved over both feet except over the fifth toe of the left foot. Plantar response normal.

X-ray negatives show no bony involvement.

Blood Examination: Red blood cells 5,000,000; white blood cells 3000; hæmoglobin 90 per cent (Sahli).

Urine: Quantity 2000 cc., 24-hour specimen; sp. gr. 1040, yellow, clear, acid, trace of albumin, 4 per cent sugar, 80 gms. per liter; no red or white corpuscles, no casts, no acetone, no diacetic acid.

Wassermann Reaction: Negative.

Ophthalmoscopic Examination: Normal fundi, no marked arterial sclerosis.

Course: Patient's tolerance for carbohydrates was found to be 60 gms. of white bread. On the eighth day he became sugar-free with a loss of six pounds in weight. At no time did acetone bodies appear in the urine. The specific gravity of the urine fell to 1030 and the total amount to 1500 cc.

In the local condition of feet there was a noticeable improvement at first as a result of rest, elevation, warm cloths, washing with peroxide and dressing with balsam of Peru.

February 12. The ulcer on the surface of the fifth toe, left foot, is healing well with rich red granulations; the one on the

dorsum has changed very little and has still a punched-out appearance.

February 19. There is a wide area of softening about the sinus on the dorsum of the left foot. Deep probing and pressure brought out about a drachm of pus. The surgical opinion is that free incision and drainage would favor healing. The ulcer on the fifth toe, left foot, is practically filled with healthy granulation tissue.

Patient left in March before his feet were entirely healed and was not heard of again until three months later. He had restricted his diet, dressed his feet carefully and rested. The ulcers were entirely healed and patient is walking about the streets daily. A 24-hour specimen of urine measured 1700 cc. and contained 2 per cent sugar and a trace of albumin, no casts, no acetone, and no diacetic acid. Three months later patient again reported. He was in good condition and working daily as a solicitor.

CASE 2 (Medical No. 22710 and 24239).—A. F., æt. 48, female, white, housewife, was admitted to the hospital June 1, 1908.

Complaint: Abdominal pain, ulcer on left foot and malaise.

Family History: No history of diabetes. A history of tuberculosis in family. Negative for rheumatism, neoplasm, or nervous affections.

Past History: General health has been fair. Patient has always been constipated. Menstruation stopped at age of 43. Has had pelvic inflammatory disease. Seven years ago her physician told her she had diabetes. She was then suffering from dimness of vision, increased hunger and thirst, polyuria, pruritus and eczema of the genitalia. Since then, patient has been in rather poor health.

Physical Examination: There is a cataract in left eye. Chest: Practically normal. Heart: Negative. Abdomen: Some tenderness in the right inguinal fossa and a palpable right kidney. Extremities: Reflexes in arms normal. Knee jerks are not obtained. Sensation over feet and ankles showed no marked disturbance. The amount of arteriosclerosis was only moderate. The left dorsalis pedis gave good pulsation, but none was obtained in the posterior tibial. Arteries on right side normal. There was no alcoholic history and no special mechanical factors, such as long hours on feet or tight shoes, played a part.

On the ball of the left great toe is an ulcer 0.5 cm. in diameter with a purulent discharge, surrounded by an indurated area. Over the dorsum of the right foot is a patch of erythema but no loss of epithelium. Scars of healed ulcers are present on ball of the right and left great toe. Area of fluctuation on dorsum of the right great toe, incised, and a bloody purulent discharge obtained. On June 3 urine showed 5 per cent sugar. Patient was made sugar-free after two days of carbohydrate-free diet. No acetone or diacetic acid appeared. By September, 1909, the patient had gained 24 lbs. and left hospital much improved, with feet healing satisfactorily.

In April, 1910, new sores on the legs and a discharging ulcer on the ball of the left great toe were noted. Patient had lost weight and had aggravation of previous symptoms. Examination showed a deep punched-out ulcer with induration and partial scab formation on the left thigh below ilium. On the right little toe and extending up the dorsum of the foot was the remains of a large bleb or bulla, the outer portion being covered with a cheesy scab. The end of the second toe showed a similar lesion.

Blood Examination: Red blood cells 4,224,000; white blood cells 10,000; hæmoglobin 82 per cent (Sahli).

Wassermann Reaction: Negative.

Patient's carbohydrate tolerance was found to be 80 gms. of white bread and complete healing of ulcers followed regulation of diet and rest.

CASE 3 (Medical No. 6916).—J. H., white, male, farmer, æt. 56, came to hospital December 11, 1896.

Complaint: Pain in stomach and swelling of ankles.

Family History: Negative for diabetes, tuberculosis, rheumatism or neoplasm.

Past History: Has been in good health most of the time, but for the last six years he has had diabetes to his own knowledge. During this period he has given more or less careful attention to his diet and been at work and fairly well, up to the last six weeks, when he began having pain in stomach, diarrhœa and swelling of legs and face.

On physical examination, enlarged heart and moderately increased blood pressure and œdema were noted. Urine showed sugar and trace of albumin. He was rendered sugar-free on a carbohydrate-free diet, but 2 to 5 per cent of sugar appeared when carbohydrates were added to his food. On January 3 a blister was noted on the left foot at the base of the great toe after rest in bed for twenty-three days. This developed into an ulcer 3 cm. in diameter with an angry-looking base. The reflexes were not obtained at either patella. There was some sclerosis of veins and the arterial walls were thicker than normal.

Sensation was not tested.

Patient had a history of very moderate use of alcohol. One drink of whiskey a day.

There was apparently no mechanical factor concerned.

The ulcer gradually healed, but three months later gangrene of both feet developed. Patient had a marked chronic nephritis in addition to his diabetes and he died in April.

CASE 4 (Medical No. 16504).—R. N., white, male, æt. 65, clerk, was admitted to the hospital November 23, 1903.

Complaint: Ulcer on toe.

Family History: Negative for diabetes, tuberculosis, neoplasm or rheumatism.

Past History: General health had always been good. No trouble from headaches, no eye, ear, nose or throat symptoms.

Cardio-respiratory and gastro-intestinal symptoms: Negative. Normal appetite. Has always drunk large amounts of water. No history of polyuria, no pruritus. Nervous symptoms: Negative.

Habits: Fairly regular. No alcoholic excess. Patient is on his feet a good deal and troubled with corns. Wears rather tight shoes.

Present trouble began about nine months ago with a corn on his right great toe which failed to improve. He finally cut and scraped it, but instead of healing, a deep ulcer developed and has persisted ever since. About five months ago 4 per cent sugar was found in his urine. From then until present time he has been on a diet and only a trace of sugar has been found since.

On physical examination the head, heart and lungs showed nothing abnormal. Abdomen was also negative. Extremities: Upper were negative, knee jerks were not elicited upon reinforcement. Sensation not tested. There was no special arteriosclerosis of the vessels of the feet. On the lower surface of the right great toe was an ulcer about 1 cm. in diameter, with a slight area of induration and very little discharge. On regular ward diet only 0.2 per cent of sugar was found. Patient remained in the hospital only a week and some slight improvement of ulcer was noted.

CASE 5 (Medical No. 16634).—White, male, æt. 48, a merchant, was admitted to hospital on February 5, 1909.

Complaint: Ulcers on feet, loss of weight.

Family History: One brother had diabetes. No history of tuberculosis, neoplasm or rheumatism.

Past History: Up to a year or so ago patient had been in good general health. Head gave him no trouble. No trouble with eyes, ears, nose or throat. Heart and lungs gave no symptoms. Bowels regular, normal appetite, no excessive thirst or hunger. He has had nó polyuria or pruritus. No nervous symptoms. About a year ago ulcers appeared on the sole of the left foot which were

aggravated by walking. They first appeared as blisters on the ball of the large toe and over the fifth metatarsal phalangeal joint. Last spring sugar was discovered in the urine and the patient has lost over fifty pounds up to time of admission. Patient has always been fond of sweets, but has had no abnormal appetite, thirst or polyuria. No alcoholic excess.

Physical Examination: Undernourished, shows signs of loss of weight. Head negative. Chest and abdomen show nothing noteworthy. Extremities: Upper are normal with slightly increased reflexes, lower show exaggerated patellar reflexes. No apparent disturbance of sensation about ankles or dorsum of feet. There is a moderate thickening of arteries. Patient was accustomed to take long walks and shoes caused some rubbing. At present there is a healed ulcer on left foot. On right are partially healed ulcers at base of great toe and over fifth metatarsal phalangeal joint. These areas are not sensitive to pressure. The skin of toes has been shed with the nails and new skin has formed beneath. With restricted diet patient was made sugar-free and ulcer had healed when he was discharged.

Case 6 (Medical No. 26022).—M. L., white, female, æt. 57, housewife, entered hospital August 10, 1910.

Complaint: Sugar in urine and ulcer on left foot.

Family History: Negative for diabetes, rheumatism, neoplasm or tuberculosis.

Past History: The patient was practically well up to three years ago when symptoms of present illness began. No trouble with head; no cardio-respiratory difficulty, digestion has been good and bowels only slightly constipated. There has been no trouble relative to genito-urinary system. Some slight nervousness but nothing outspoken. Habits have been good with no history of alcoholic excess. Patient is on her feet only about the average amount. She admits wearing tight shoes.

Present illness began three years ago with polydipsia, polyuria, pruritis vulvæ, double vision and attacks of hemianopia. Accompanying these symptoms discoloration of certain small areas at points of pressure from shoes appeared on both feet. These spots would partially clear up and again reappear as general symptoms varied. Sugar was found in the urine and for the last six years a fairly strict diet was used for short periods. with improvement while it was maintained. For several months, about a year before admission, patient says that she had a small superficial ulcer on the right great toe which healed rapidly as her general condition responded to a careful dietary. The present ulcer on the left great toe has existed for six or seven months, and recently there has been a sero-purulent discharge from it, but it gives no pain.

On examination the patient was found to be undernourished; pallor striking. The head was practically negative. Eye grounds showed no evidence of hæmorrhage or exudate. No diabetic retinitis. There was nothing abnormal made out in chest or in abdomen. Extremities: Arms showed no weakness and reflexes were present. The reflexes of legs were present but rather sluggish. The sensation over the legs and dorsum of the feet was intact. The blood vessels showed moderate thickening. The dorsalis pedis and posterior tibial arteries pulsated in both feet. On the left foot at point of pressure under the ball of the great toe is a large punched-out ulcer with clean, moist base, precipitous edges and some induration. No pain was caused in probing the ulcer. No sinus was found, but a purulent discharge welled up on pressure. The ulcer was dressed with usual local applications daily but healing did not progress at all satisfactorily. The carbohydrate tolerance was determined to be 40 gms. of white bread. Urine 1000 to 2000 cc. daily, no acetone or diacetic acid appeared. X-ray examination revealed a chronic osteomyelitis of the first left metatarsal bone and the toe was amputated. Recovery was rapid.

Case 7 (Medical No. 26411).—A. C., colored female, æt. 60, housewife, admitted to hospital October 21, 1910.

Complaint: Loss of weight and a sore spot on heel.

Family History: No diabetes, no tuberculosis, no neoplasm, no rheumatism.

Past History: Unimportant up to two years ago when symptoms of the present trouble began, with loss of weight and easy exhaustion. She kept about her work but has steadily grown worse. Two weeks before admission she began having excessive thirst and took a small amount of whiskey each day. She noticed frequent micturition and the passage of large amounts of urine at each voiding. Her right leg became numb and tingled and a sore spot appeared on the right heel.

Examination: Physical unimportant except for the lower right extremity. The leg showed some hyperæsthesia especially about the heel. There was some sclerosis of arteries and the dorsalis pedis and posterior tibial were felt with difficulty. The patellar reflexes were absent.

The right heel shows a small hæmorrhagic area covered by thin unbroken skin. There is very little induration to be made out. The carbohydrate tolerance was found to be high—200 gms. of white bread, and no diacetic acid or acetone appeared. When patient was discharged there was still some redness about heel, but the pain and tenderness had left.

The exact etiology of *malum perforans* is still undetermined, although one does not have to look far for theoretical explanations. Several authors believe the ulcer depends upon changes in the peripheral nerves. Against this view, however, is the fact that the sensory disturbances are slight; further, the ulcers do not present the same picture as that seen in known forms of chronic neuritis. There is not, in the literature, a well-authenticated case of diabetic *mal perforant* due to neuritis. Neural change may be secondary rather than primary. The mechanical factor is apparently of some etiologic importance and has its supporters. This mechanical theory holds that the ulcer is due to the constant pressure exerted on certain parts of the feet in walking or standing. In favor of the theory is the marked improvement which, in some cases, follows upon rest in bed and removal of pressure. Against this theory is the stubborn refusal of some ulcers to heal in spite of the best local treatment. It would seem that the mechanical factor can not be more than a contributory cause. A third theory offers vascular change as the primary cause of perforating ulcer. In a majority of the cases no arteriosclerosis, or only a slight grade, exists in the vessels leading to the part affected. Endarteritis obliterans must be borne in mind. It, however, develops secondarily in the course of *mal perforant* and may be absent in some cases altogether. Vascular change, therefore, like pressure, may be a contributory factor but will not, alone, explain the lesion. The view that the true cause lies in a disturbance of tissue vitality due to the existing hyperglycæmia seems a rational one. As a result of this lessened tissue resistance one might well explain the frequent appearance of furuncles, carbuncles and gangrene; as a rule, improvement of glycosuria and ulcer are coincident.

The approximate frequency of the occurrence of *mal perforant* in diabetes may be judged from the following: Naunyn reported 7 in 100 cases, Williamson[5] 4 in 140 cases, and at The Johns Hopkins Hospital there have been 7 in 275 cases. Fitz and Joslin[6] report that at the Massachusetts General Hospital from the year 1824 to 1898 there were admitted to the wards 172 diabetics; only one case of round ulcer is recorded, and this improved under treatment. Among 687

diabetics, therefore, there were 19 with perforating ulcers, or 2.7 per cent. Gascuel,[7] 1890, found among 91 cases of *mal perforant* of all types 14 cases of diabetes, *i. e.*, 15 per cent.

Perforating ulcer occurs in the male vastly more often than in the female. Men are of course more exposed to trauma and to chronic irritation of the feet. Alcohol is used to a greater extent by men, but it has not been shown to have any definite causal influence.

Nearly every case recorded in the literature has occurred in an individual over forty years of age. It is a malady, therefore, of middle, or of late life.

The glycosuria in these cases is almost always of a mild grade. Scarcely an instance of severe glycosuria with *mal perforant* is to be found in the literature. Naunyn cites a possible exception in the patient described by Buzzard[8] in whom there was 4 to 5 per cent of sugar in the urine on a slightly restricted diet; still the total amount of urine voided in the twenty-four hours was not over two liters. The mild nature of the diabetes may be in part dependent upon the fact that perforating ulcer occurs in elderly people. All of Naunyn's 7 cases, save one, were over forty; all 4 of Williamson's cases were over fifty; and all 7 of our cases were over forty-five years of age.

The *mal perforant* of diabetes resembles very closely in appearance that of tabes, but is to be distinguished from it, and from other forms of ulcer, by the location of the lesion. According to Naunyn, and from our own case reports, the diabetic perforating ulcer occurs more often than not at an "atypical" place. In one of Naunyn's cases (No. 79, p. 268) the ulcers were on the right index and little fingers; in another (No. 81, p. 271) the ulcer was on the lateral side of the foot, just under the external malleolus. In our cases, similar examples are to be found (see case reports).

The initial lesion is often in the form of a small vesicle which later develops into an ulcer, or the process may take its origin from an infected corn. The condition may be superficial, limited to the shin and subcutaneous tissues, or it may extend more deeply, involving bone or cartilage, or opening into a joint. The metatarsal phalangeal joint is a favorite seat for such a pathological change. The superficial ulcer tends to heal in a short time when submitted to the proper treatment (Cases 1 and 2 of our series) while the ulcer of the deep, burrowing type is prone to last for a considerable period (Case 6). Sequestra are rarely expelled. There should be no confusion, as a rule, between perforating ulcer and the progressive ulcerations of diabetic gangrene. The former rarely, if ever, spreads out upon the surface, which is in sharp contrast with the behavior in gangrene. However, confusion does sometimes arise, and there are also cases in which perforating ulcer is associated with a deep seated phlegmonous inflammation and gangrene. Naunyn believes that febrile manifestations in *mal perforant* speak for an associated infectious process arising in the ulcer

Anæsthesia of the ulcer and its surrounding tissue may occur in diabetic *mal perforant*, but it is no more constantly seen than in non-diabetic cases. We have not found it outspoken in any of our cases.

The knee jerks apparently differ in individual cases. Williamson found them absent bilaterally in two of his 4 cases, and absent on one side in a third case. In our series of 7 cases the knee kicks were absent in 4, and present in 3 cases.

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NOTES AND NEWS.

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Dr. Paul G. Woolley is Director of the Laboratories of the Cincinnati Hospital and Dean of the Faculty of Medicine, Ohio Miami Medical College.

Professor Ludwig Aschoff, of the University of Freiberg in Breslau, Germany, has accepted an invitation to deliver the Cartwright lectures of the Alumni Association of the College of Physicians and Surgeons, New York, between March 15 and 20, 1913. The exact date and subjects of the lectures will be announced later.

The American Surgical Association has appointed a committee consisting of Drs. William L. Estes, South Bethlehem, Pa.; Thomas W. Huntington, San Francisco, California; John B. Walker, New York City; Edward Martin, Philadelphia; and John B. Roberts, chairman, 313 S. 17th Street, Philadelphia, to report on the operative and non-operative treatment of closed and open fractures of the long bones and the value of radiography in the study of these injuries. Surgeons, who have published papers relating to this subject within the last ten years, will confer a favor by sending two reprints to the chairman of the committee. If no reprints are available, the titles and places of their publication are desired.

JOHN B. ROBERTS, *Chairman.*
313 S. 17th St., Philadelphia, Pa.

NEW PUBLICATIONS.

The individual papers which make up the volumes of The Johns Hopkins Hospital Reports will in future also be published as Monographs and put on sale by The Johns Hopkins Press. The first three, to appear shortly, are:

Free Thrombi and Ball Thrombi in the Heart. By J. H. Hewitt, M. D.

Primary Carcinoma of the Liver. By M. C. Winternitz, M. D.

Benzol as a Leucotoxin. By Laurence Selling, M. D.

ARMY MEDICAL CORPS EXAMINATIONS.

The Surgeon General of the Army announces that preliminary examinations for the appointment of First Lieutenants in the Army Medical Corps will be held on January 20, 1913, at points to be hereafter designated.

Full information concerning these examinations can be procured upon application to the "Surgeon General, U. S. Army, Washington, D. C." The essential requirements to securing an invitation are that the applicant shall be a citizen of the United States, shall be between 22 and 30 years of age, a graduate of a medical school legally authorized to confer the degree of Doctor of Medicine, shall be of good moral character and habits, and shall have had at least one year's hospital training as an interne, after graduation. The examinations will be held simultaneously throughout the country at points where boards can be convened. Due consideration will be given to localities from which applications are received, in order to lessen the traveling expenses of applicants as much as possible.

The examination in subjects of general education (mathematics, geography, history, general literature and Latin) may be omitted in the case of applicants holding diplomas from reputable literary or scientific colleges, normal schools or high schools, or graduates of medical schools which require an entrance examination satisfactory to the faculty of the Army Medical School.

In order to perfect all necessary arrangements for the examination, applications must be completed and in possession of the Adjutant General at least three weeks before the date of examination. Early attention is therefore enjoined upon all intending applicants. There are at present thirty-five vacancies in the Medical Corps of the Army.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.